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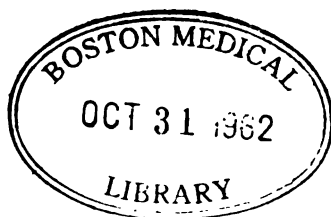
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ALIMENTARY TRACT

HYSTERICAL DYSPHAGIA*

PORTER P. VINSON

Many references are found in medical literature to various hysterical manifestations, but I have been unable to find a description and discussion of a group of cases in which a hysterical inability to swallow is the predominating and sometimes the only symptom. From the records of the Mayo Clinic I have been able to collect sixty-nine such cases. Fifty-seven of the patients were females, and twelve were males. Patients having the ordinary "globus hystericus" are not included in the series, since they rarely, if ever, have any definite obstruction to food and none of them shows the marked nutritional disturbances seen in many of the patients selected for study.

The dysphagia usually began suddenly and in many instances the patients dated the onset of their symptoms from a time when they choked on a piece of solid food, the point of obstruction being high in the throat. This was followed by an inability to swallow solid food, particularly meat and green vegetables, and difficulty in swallowing pills or capsules. Liquids and soft foods were usually taken well, and the loss of body weight was not marked. A moderate or marked secondary anemia developed, probably due to the quality of the food taken.

Thirty-seven of the patients had a hemoglobin of 60 per cent or under; the lowest was 27 per cent. Enlargement of the spleen, usually quite marked, was noted in twelve cases. The duration of symptoms varied from one month to twenty-five years. Anemia was more liable to be present in cases in which the history of dysphagia was long standing. Roentgenographic examinations were made in all the cases with negative results; esophagoscopic examinations that were made revealed no lesions.

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TREATMENT

The treatment consisted in passing a plain esophageal sound, the size immaterial, into the stomach, guided by a previously swallowed silk thread. The treatment was purely suggestive as there was no real stretching of the esophagus. The patients were encouraged to eat solid foods, and were given Bland's pills and Fowler's solution. Usually nothing further was necessary to bring about an immediate temporary cure. The blood picture improved at once, and if symptoms did not eventually recur it became normal. The spleen returned to normal size.

Prolonged observation of many of these patients demonstrated gratifying results. Recurrences, which may occur unless the patients are constantly reassured with regard to their condition, are usually in patients who have other hysterical manifestations. In case of recurrence a second passage of the sound will relieve for an indefinite period of time.

Hysterical dysphagia must be distinguished from all lesions producing dysphagia, but the lesion of fairly frequent occurrence with which it might easily be confused is a slow growing carcinoma at the introitus. The long duration of symptoms with absence of obstruction to the sound is usually enough to determine the diagnosis. In case of doubt, an esophagoscopic examination can be made without trouble.

An interesting feature in these cases is that after the dysphagia is relieved and food is being taken freely a moderate degree of hypothyroidism may develop, necessitating the regular administration of thyroxin. Plummer, who first pointed out this complex of dysphagia, without organic obstruction, anemia and enlargement of the spleen, suggests that during the long period of inanition a light demand for thyroxin results in a disuse atrophy of the thyroid and, hence, following the relief of the dysphagia, the thyroid may not be able to meet the demand of the body.

CONCLUSIONS

1. Although hysterical dysphagia is a functional disorder, the prolonged unbalanced diet gives rise to enlargement of the spleen and secondary anemia.

2. Normal deglutition can be restored by passing an esophageal sound.

3. Recurrences are liable to occur, but can be relieved by further passage of sounds and by constantly reassuring the patient.

4. When normal deglutition is restored, the blood picture returns to normal, and the splenic enlargement subsides.

5. Hypothyroidism may develop after the patient begins to swallow freely, due to the inability of the thyroid to furnish secretion enough to care for the increased food intake.

ESOPHAGEAL STRICTURE FOLLOWING THE VOMITING OF PREGNANCY*

PORTER P. VINSON

In reviewing the literature of benign strictures of the esophagus I have been unable to find any reference to a type of stricture that occurs during pregnancy, and usually the result of pernicious vomiting. Six such cases have been observed in the Mayo Clinic since 1911, and since the condition is apparently quite unusual a full report of these cases seems justifiable. Probably such strictures occur occasionally, but the association with the vomiting of pregnancy has not been considered.

Many cases of spontaneous rupture of the esophagus following prolonged periods of vomiting have been reported and it is quite probable that the strictures in our cases were caused by the same factors. Whether or not esophagomalacia, described by Zenker and von Ziemsen in 1878, is responsible for the condition is of course debatable. All of their cases occurred in males, who had induced vomiting over long periods of time. No reference was made to a similar condition in females.

REPORT OF CASES

Case A55895. Mrs. J. B., aged forty years, was examined July 12, 1911. The patient had five children living and well. In all her pregnancies she had had heartburn with belching of gas. Her last pregnancy began in May, 1910 and December 9, 1910 she began to vomit. Within a day or two substernal pain developed. Deglutition seemed to be free, but everything was vomited for a week, the pain becoming so severe that morphin was necessary to control it. However, the act of swallowing did not increase the pain. During the following week she managed to keep milk down and had but little pain. December 24, beef tea was taken and this brought on pain and vomiting. December 25, she aborted. For the next week the swallowing of solid food brought on the substernal pain with dysphagia; the food seemed to stick in the lower esophagus. Within a few days the esophagus closed completely with cessation of pain. Soon after the closure she spat up some purulent material. A physician was called and he tried to pass a stomach tube, but met obstruction and the patient expectorated pus and blood. The physician believed that a lung abscess had ruptured into the esophagus. A gastrostomy was performed February 4, 1911, following which the patient was able to take food. The stricture remained patent for a week and then closed so that nothing was taken by mouth. Repeated efforts to have the patient swallow a thread failed.

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At the Clinic the patient was esophagoscoped and the stricture located 27.5 cm. from the incisor teeth. After dilatation a thread was swallowed and in two months the stricture had been dilated to 32 F. The patient was allowed to return home. Dilating olives are passed at long intervals and the patient rarely experiences any dysphagia.

Case A86731. Mrs. H. W. R., aged thirty-three years, came to the Clinic June 26, 1913. She had had two pregnancies; both children were living; one was ten years and one three months of age. One miscarriage had occurred one year before examination. The patient had expected to be in labor the middle of April, 1913. The latter part of March she began to have sour stomach, but no more than with her former pregnancies. April 4, she ate a heavy meal. That night she began to hiccup and had severe pain in the stomach. This continued for three days, after which she vomited. The vomitus consisted of food eaten April 4. Hiccups continued a few days longer and then vomiting of dark, sour material with "coffee grounds." This lasted until labor was induced April 11. The stomach was washed for a few days, which stopped bleeding and relieved the pain which had been constant since April 4, and then vomiting occurred only when food was taken. April 18, the patient suddenly fainted and passed tarry stools. A diagnosis of hemorrhage was made. The patient began to gain and was able to eat soft foods. May 1, dysphagia began with pain at the cardia and became so marked in a few days that for six weeks before the patient came to the Clinic only very little liquid entered the stomach and she became very weak.

July 1, 1913, gastrostomy was performed and later the stricture was gradually dilated. A specimen removed from the lesion proved to be granulation tissue. The patient was dismissed in August, 1913, able to eat anything. She developed typical pellagra after going home, but she recovered after a time and in a recent letter states that she is in very good condition.

Case A163060. Mrs. A. M. B., aged thirty years, was examined June 16, 1916. At the time of pregnancy thirteen months before she had been nauseated and had vomited during the first three months, and again in the seventh month, when she vomited dark, bloody material for a week; the vomiting was accompanied by epigastric pain. Uremia set in and labor was induced. For the past ten months (three months after labor) she had complained of intermittent difficulty in swallowing, but without enough obstruction to interfere with nutrition. At the onset dysphagia was more marked with the swallowing of fluids than of solids.

Roentgenograms showed what appeared to be a transitory spasm at the juncture of the middle and lower third of the esophagus. An obstruction was located 5 cm. above the cardia and was dilated with ease to 35 F. with complete relief from dysphagia. Further dilatations were made. The patient has not been heard from since she returned home.

Case A189530. Mrs. J. K., aged thirty-four years, was examined March 28, 1917. The patient had been pregnant three times and during the last pregnancy, which began in May, 1916, she was more than usually nauseated. During the last month of pregnancy she vomited large quantities of dark colored material. She had pain in the epigastrium and a slight rise in temperature. A normal child was born at term. Following the delivery the mother collapsed completely, but responded to saline hypodermoclysis and in the course of a week her temperature was normal. Her mind was unbalanced for three or four days. She continued to vomit almost all food taken and lost 62 pounds in weight; the vomitus was not dark in color. For three weeks before examination obstruction had been almost complete. She did not have pain or dysphagia, but a sense of heaviness, and distress which was relieved as soon as food was vomited.

A gastrostomy was performed March 31. The patient died April 8. Postmortem examination revealed a lesion beginning at the cardiac opening of the stomach and extending upward for 7.5 or 10 cm. The esophageal lining was hyperemic and edematous.

The walls were markedly thickened, indurated, and hyperemic. Behind the esophagus, between it and the aorta, at about the level of the sternal end of the third rib was a diffuse area of acute inflammation containing about 8 c.c. of pus. The blood culture ante mortem showed a growth of green-producing streptococcus. There was a small abscess in the left breast and an organized thrombus of the left uterine artery.

Case A215797. Mrs. P. McM., aged forty-nine years, was examined December 5, 1917. She had been married twenty-seven years; she had three living children; four children were dead and there had been three miscarriages. During pregnancy twenty-three years before examination the patient had vomited frequently. Following delivery she began to have dysphagia and pain on swallowing. Food seemed to stick in the lower esophagus. Frequent rectal feeding was resorted to, and the patient gradually seemed to get a little stronger. Pain was so severe and constant that morphin was used freely and the patient contracted the morphin habit. Finally the home physician dilated the stricture with rubber dilators with much benefit, but not complete relief.

On examination the obstruction was found to be 30 cm. from the incisors; the stricture was dilated to 50 F. with ease. A recent letter states that the patient is in good condition.

Case A326626. Mrs. C. F. R., aged thirty-five years, was examined July 27, 1920. She had been married twenty months and became pregnant two months after marriage. During the entire period of pregnancy she was severely nauseated and vomited, and finally at the end of the eighth month (September, 1919) the uterus was emptied of a dead macerated fetus. About a month later when she began to take solid food she noticed dysphagia; this grew gradually worse. A diagnosis was made of esophageal stricture and several unsuccessful attempts were made to pass instruments through the esophagus.

A gastrostomy was performed March 15, 1920. Following this the patient gradually lost the ability to swallow food and for three to four weeks before coming to the Clinic she was unable to take any nourishment by mouth.

August 3, 1920, the patient was esophagoscoped. A small funnel-shaped stricture was located and dilated to 31 F. The patient was then able to swallow easily. Further dilations were employed using a swallowed silk thread as a guide. The patient was dismissed August 28, 1920; she continues to do well with dilatations at home from time to time.

BENIGN AND MALIGNANT GASTRIC ULCERS FROM A ROENTGENOLOGIC VIEWPOINT*

RUSSELL D. CARMAN

Notwithstanding the high efficiency of the roentgen ray in the diagnosis of gastric cancer and gastric ulcer, I have at various times pointed out that the roentgen-ray examination does not always determine the benignancy or malignancy of a given ulcerous lesion. As exceptions to this view have occasionally been expressed I believe that a broader discussion of the question may contribute to still greater concord of opinion.

Roentgenologic distinction between typical cancer and typical ulcer is manifestly not difficult. One is a tumor mass intruding on the gastric lumen, the other is an excavation in the gastric wall. Correspondingly, the visualized gastric chamber shows a local diminution, a filling defect, in the former, and a local expansion, a niche, in the latter. One is plus, the other minus. These lesions are easily diagnosed; many are operated on and for the most part adequately proved.

From a pathologic standpoint this classification is rather diagrammatic. Between the classic tumor and the classic ulcer are innumerable gradations according to the predominance of one or the other feature. At operation are found ulcerating cancers, ulcers which contain a minority of cancer cells, and benign ulcers with or without surrounding tumefaction.

Roentgenologically we are obliged to group these lesions in two general diagnostic classes, the tumorous and the ulcerous. The tumorous lesions are commonly diagnosed by the roentgen ray as cancer, because experience has taught that nearly all the gastric tumors are carcinomatous. The ulcerous lesions are reported by the roentgenologist as ulcers because the characteristic niche-deformity is within the wall of the stomach. When they are exposed at operation they gen-

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erally have the macroscopic appearance of benign ulcer, but microscopic examination of tissue from the ulcer sometimes reveals cancer.

Ulcers which show microscopic evidence of cancer may be divided into two types. In one type both the border and the floor of the ulcer contain cancerous tissue in abundance (Fig. 1). These are generally believed to be ulcerating cancers which were malignant from the beginning. This was the opinion of Hauser who stated that in a pri-



FIG. 1 (Case A206304).—Malignant ulcer, niche type. Cancer in floor and margin.

mary cancer-ulcer constantly the entire border and floor are more or less infiltrated with cancerous tissue, inasmuch as the infiltration precedes the ulceration. In the second type the floor of the ulcer does not contain cancer, but cancer is found in the ulcer margin (Fig. 2). This type has been given especial attention in connection with the development of cancer on ulcer, a theme which has stimulated an extensive literature.

Many articles have been published by clinicians, surgeons, and

pathologists representing every shade of opinion from that of Hirschfeld, who denied any relation at all between gastric cancer and ulcer, to that of Zenker who held that most gastric cancers develop on ulcer.^{1, 4, 5, 7, 9, 10, 11, 12, 13, 14, 16, 17, 20, 21, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 40, 41, 42, 43}

Except Hirschfeld, who seems to be alone in his view, all agree that cancer may develop on ulcer, and only the frequency of such development is in controversy. Regardless of the issue of this debate, it is difficult to escape the conclusion that any ulcer is a potential cancer. The obvious corollary is that treatment should be surgical and the ulcer excised or destroyed.



FIG. 2 (Case A346077).—Malignant ulcer, niche type. Cancer found over an extent of 3 mm. only, in margin.

Many malignant ulcers, particularly those containing small amounts of cancerous tissue, appear to be ulcers simply and solely, as seen by roentgenologists, clinicians, and surgeons. Abundant evidence can be gathered to substantiate this claim. Surgeons and pathologists see these lesions daily and have learned that they cannot depend on a gross examination to determine whether they are malignant or benign. W. J. Mayo says, "Even at operation it is sometimes difficult to determine whether the condition is cancer or ulcer . . . until a specimen is secured for microscopic examination." In a report of a number of such

lesions, Wilensky and Thalheimer say, "In all these it was not possible to make the diagnosis of malignancy from the gross appearance of the specimens as they were observed at operation." Even in those adjudged to be benign the microscopic diagnosis, they state, was arrived at with difficulty in a few because of atypical hyperplastic forms at the margin.

Ewing has made the statement, "In my own material I have had much difficulty in deciding how to interpret some ulcerating and cancerous lesions."

Küttner states, "In many cases it is not possible, either clinically or with the abdomen open, macroscopically to differentiate callous ulcer from cancer. The microscopic examination alone makes the differential diagnosis."

Payr, likewise, states, "Clinically, historically, and even after thorough macroscopic examination of the specimen a case may appear to be one of quite typical ulcer, and the subsequent histologic examination first tells us, in an unequivocal way, the unpleasant fact that a beginning or advanced cancer is present."

Orth remarks that the macroscopically ulcerous appearance can never be relied on.

MacCallum has seen typical round ulcers, in the margins of which carcinomatous growth of epithelium of unmistakable character was found, although the tumor had not developed sufficiently to disturb the characteristic appearance of the ulcer.

Aschoff asserts that often only the microscope can determine whether or not a cancerous ulcer is present, and that the microscopic distinction is not always easy.

Henke believes that to determine macroscopically without sectioning whether a callous gastric ulcer is or is not cancerous is impossible in many cases.

From the roentgenologic standpoint Clairmont and Haudek write as follows: "Although many criteria make it possible to differentiate cancer from ulcer, this distinction is risky in a certain group of cases well diagnosed as chronic ulcer, whose transition into cancer cannot be excluded. . . . Since at laparotomy the surgeon has difficulty in making the differential diagnosis macroscopically, since both diseases cause infiltrated glands, indeed since the histologic examination must be conducted most thoroughly in order not to overlook small groups of cancer cells, it can be understood that here roentgen diagnosis must

find a limit." Again, they state, "The wide consensus of view that a chronic ulcer should have surgical treatment makes its differentiation from cancer superfluous. Certain is it that thereby many times the generation of a cancer will be prevented."

All this testimony is fairly representative of the mass of opinions and indicates the vanity of any hope we might have entertained that

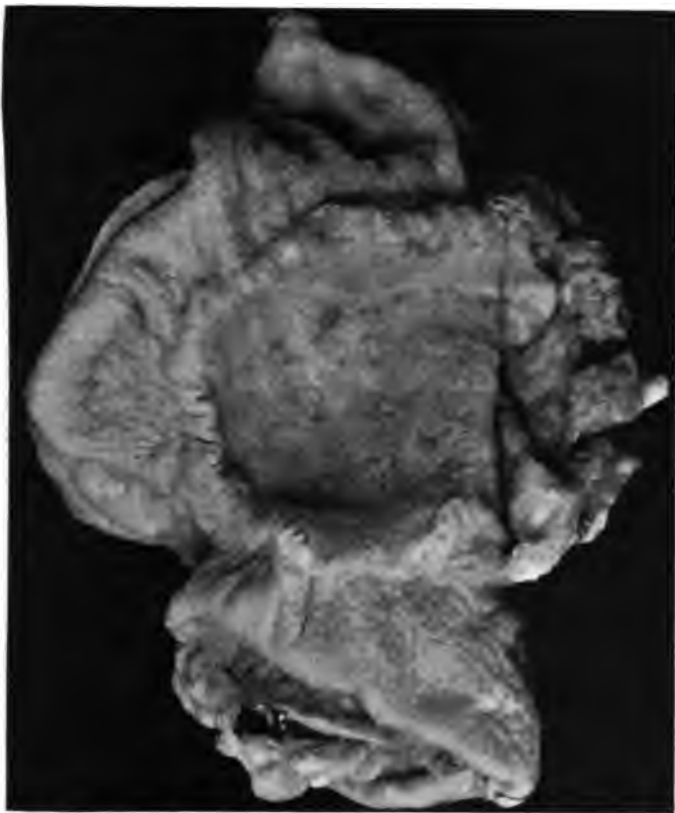


FIG. 3 (Case A262866).—Ulcerating cancer. Large deep ulcer with overhanging margin. This is the type of ulcer whose crater may be seen as a meniscus during fluoroscopy.

the roentgen examination may succeed in a task which is sometimes difficult for the microscope.

MacCarty has said, "If the surgical pathologist cannot always distinguish grossly simple, chronic, gastric ulcers from carcinomatous gastric ulcers, it is impossible for surgeons, roentgenologists and

clinicians to make the differentiation with their lesser instruments of observation, there being no specific clinical or laboratory test for early cancer."

Conceding the justice of my colleague's criticism from the strict point of view of the pathologist, I believe, nevertheless, that to impose such limitations of diagnostic latitude would, under present conditions, impair the practical efficiency of the roentgen-ray examination. With the increased capability of the roentgen ray, clinicians and surgeons place correspondingly increased reliance on it, not only for the demon-



FIG. 4 (Case A166828).—Ulcerating cancer, having the same characteristics as the one shown in Figure 3.

stration of gastric lesions but also for the determination of their probable character. That this reliance has not been entirely misplaced is, I believe, abundantly proved. On the other hand, I do not recommend or practice diagnosis on mere suspicion. All conclusions from the roentgen examination should be well reasoned, and the examiner should not be expected to give information which he cannot possibly obtain.

It would seem that the roentgenologist is between two fires. On one side is the clinician who desires a maximum of diagnostic detail,

and on the other is the pathologist who insists that the roentgen ray can furnish only a minimum of positive information.

At the roentgen laboratory of the Mayo Clinic we report the well defined ulcerous gastric lesion of the niche type as "ulcer," because in its gross characteristics it is an ulcer, and the examiner's associates understand very well that he cannot determine whether its histologic



FIG. 5.—Drawing illustrating the demonstration of the lesion by palpation during roentgenoscopy.

structure is benign or malignant. Likewise, a gastric filling defect with a palpable tumor is reported by us as "cancer," because experience has shown that 95 per cent of such tumors are cancers, and the empirical element in the diagnosis is thoroughly comprehended by all concerned. But when the clinician is not thoroughly acquainted with the roentgenologist's method of examination and his manner of expressing the results the latter should report his diagnosis in guarded terms. A lack

of caution in this respect adds to the doubt of those who view roentgen diagnosis with skepticism.

As I suggested at the beginning of this paper some ulcerating cancers have the gross characteristics of both ulcer and cancer (Figs. 3 and 4). When a cancer has undergone deep ulcerous excavation and the ulcer is surrounded by a wall-like overhanging margin it may present certain roentgenologic peculiarities which I have recently described⁶ and which I consider pathognomonic. Fluoroscopic examination is required to elicit these characteristics because palpatory manipulation is

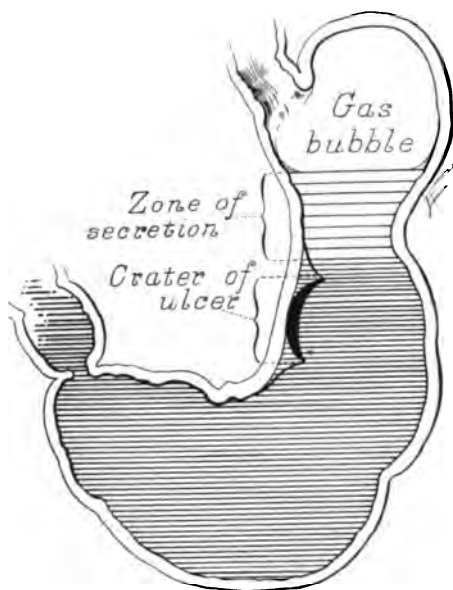


FIG. 6.—Drawing illustrating meniscus-like appearance of crater seen in profile. Ulcer on the posterior wall near the lesser curvature.

indispensable (Fig. 5). The picture thus obtained varies slightly with the site of the ulcer.

If the lesion is on the vertical portion of the lesser curvature or on the posterior wall near the lesser curvature, approximation of the walls of the stomach by palpation causes the crater of the ulcer to appear on the screen as a dark shadow resembling a meniscus as seen in profile (Fig. 6). The convexity of the meniscus is directed outward toward the gastric wall and its concavity toward the gastric lumen. When the ulcer saddles the lesser curvature of a fishhook stomach distal to the incisura angularis, the floor of the ulcer bends with the lesser curva-

ture and its concavity is directed outward (Figs. 7 and 8). If the ulcer is high in the stomach on the posterior wall, well away from the curvature, thinning the barium by manual pressure reveals the crater as a somewhat rounded dense shadow encircled by a lighter zone, but no crescent is seen, as when viewed edgewise (Fig. 9). By turning the patient into the lateral view and palpating the stomach the meniscus-like appearance of the crater of the ulcer as seen in profile may



FIG. 7 (Case A365132).—Roentgenogram of ulcerating cancer saddling the lesser curvature at the pyloric end of the stomach. Irregularity of greater curvature due to spasm (Specimen, Figure 8).

sometimes be obtained. It will be understood readily that other modifications of this sign may result from variations of the pathologic condition or situation of the lesion. For example, the floor of the ulcer may be flat instead of curved and show in profile as a straight line. The manner of palpation and degree of pressure exercised also affect the outline of the visualized crater, so that it may appear rectangular or biconcave, or otherwise.

Briefly summarized, the visualized crater of this ulcer differs from

the classic niche type in three particulars: (1) the crater is not within the wall of the stomach and therefore does not project from the visualized gastric lumen, (2) in profile the crater appears as a meniscus; and (3) it tends to retain its barium content during palpatory maneuvers and is not easily emptied (Fig. 10).

For two or three years I have been observing ulcerous lesions with the foregoing characteristics. Operative and pathologic findings, both



FIG. 8.—Same case as in Figure 7. Ulcer sectioned through the lesser curvature showing half of the crater. Note the thick indurated base and overhanging margin.

gross and microscopic, have consistently verified the diagnosis of cancer.

On the other hand, the niche type of ulcer (Figs. 11 and 12) produces virtually the same roentgenologic manifestations whether it is benign or malignant, and any prediction of its probable character based on the roentgen-ray findings is hazardous (Figs. 13 and 14).

Large size of the ulcer crater is one indication of malignancy. When the niche representing the crater is 2.5 cm. or more in diameter,



FIG. 9.—Drawing. Ulcerating cancer of the posterior wall. Appearance of the crater at roentgenoscopy on palpation.

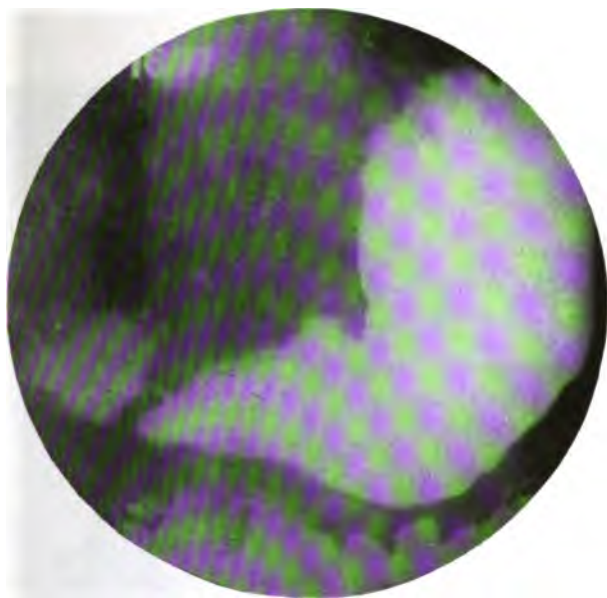


FIG. 10 (Case A371607).—Roentgenogram negative. Ulcerating cancer on the posterior wall of the middle portion of the stomach, near the lesser curvature. Meniscus-like crater seen at roentgenoscopic examination.

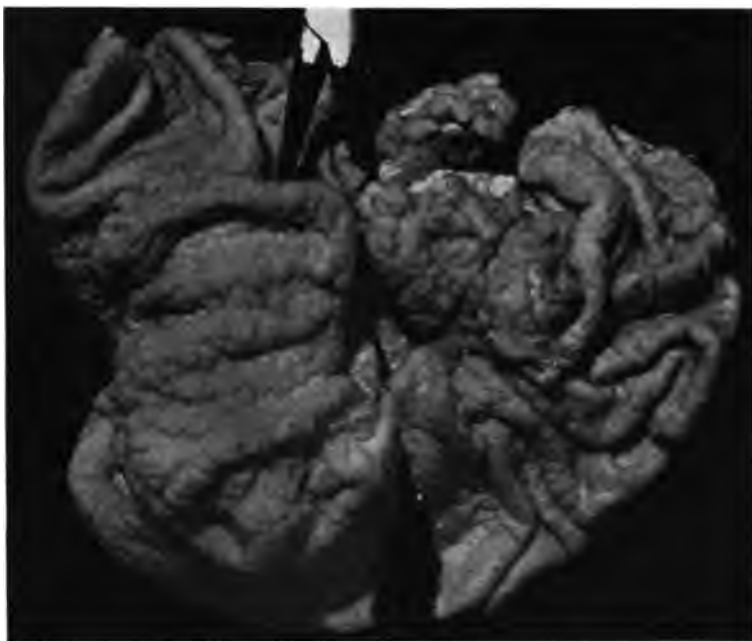


FIG. 11 (Case A346953).—Benign ulcer. Note similarity to Figure 12.



FIG. 12 (Case A292220).—Malignant ulcer. Compare with Figure 11.

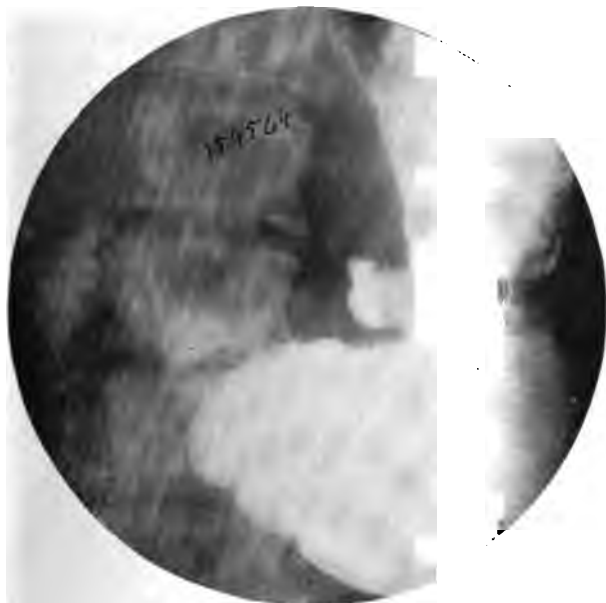


FIG. 13 (Case A154564).—Roentgenogram. Niche type of ulcer, benign. Compare with Figure 14.



FIG. 14 (Case A116521).—Roentgenogram. Niche type of ulcer, malignant.

cancer is usually found in the ulcer on microscopic examination (Fig. 15). Unfortunately a smaller ulcer may also be carcinomatous, or exceptionally a larger one may be benign.

In this connection it should be mentioned that a perforated ulcer producing an accessory pocket, no matter how large, is seldom malignant. It is true that an ulcerating cancer may break through the gastric wall and attach itself to adjacent tissue, but filling defects suggesting the presence of a tumor are also likely to be seen.



FIG. 15 (Case A20799).—Roentgenogram. Niche type of ulcer. Niche extraordinarily large. Operation. Cancer demonstrated microscopically.

A marked filling defect or gross deformity of the gastric outline adjacent to a niche may suggest malignancy. Such deformities, however, are most often due to induration, perforation, adhesions, or spasm accompanying a benign ulcer.

Other minor manifestations of benign and malignant niche ulcers give little or no aid in the effort to distinguish between them. Cancers which are not mechanically obstructive are commonly associated with achylia and a gaping pylorus, while benign ulcers, even though distant from the pylorus, are likely to be accompanied by hyperacidity, spasticity of the pylorus, and six-hour retention. But such findings are not

constant in either variety of ulcer, and only slight weight can be attached to them.

The broad incisura of cancer and the narrow incisura of ulcer, both of which are contractures of the greater curvature in the plane of the lesion, depend on the extent rather than on the character of the lesion. Thus, while a broad incisura would correspond to an extensive lesion which because of its size is open to the suspicion of malignancy, the small ulcer with a narrow incisura is not wholly exempt from mistrust.

Alterations of peristalsis are of trifling differential significance. A gross malignant ulcer is more often associated with anacidity and peristaltic sluggishness, a simple ulcer with hyperacidity and peristaltic vigor, but the reverse may occur, and it would be folly for the examiner to be influenced by the peristalsis observed.

SUMMARY

There are but two varieties of ulcerous gastric lesions which evince any noteworthy roentgenologic indications of malignancy. One is the ulcerating cancer with the meniscus-like crater. The other is the niche type of ulcer with an unusually large crater. With these exceptions the examiner cannot venture opinions as to the probable character of ulcers revealed by the roentgen ray, nor should he be expected to do so. Any ulcer which appears to be benign macroscopically may prove to be malignant microscopically. Cancer may arise in an ulcer which was primarily benign.

However interesting and important these facts may be to roentgenologists, clinicians, surgeons, and pathologists, they are vastly more important to the patient, whose welfare should be our first consideration.

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BENIGN TUMORS OF THE STOMACH: REPORT OF TWENTY-SEVEN CASES*

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Benign new growths of the stomach, which because of their size or position may cause disturbed gastric function are rare enough to be regarded clinical curiosities. In fact the great preponderance of gastric cancers over benign tumors of the stomach largely explains why the latter receive scant consideration in the differential diagnosis of doubtful cases. A preoperative diagnosis of benign gastric neoplasm is exceedingly difficult in the majority of cases, and has rarely been made at least until very recently. A great many of the cases reported in the literature have been found at necropsy, and in the majority of those found at operation, the true nature of the lesions had not been determined beforehand. In view of the importance of surgical conservatism in such a useful organ as the stomach the possibility that new growth is benign takes on a very practical aspect. Of further clinical and diagnostic importance is the fact that these tumors may cause complications such as pyloric obstruction, intussusception of the stomach into the duodenum, recurring severe gastro-enteric hemorrhage, strangulation, severe colic, malignant degeneration, and even perforation.

Two instructive reports on this subject have been presented before this association by the late Dr. Jesse Myer and by Basch. For additional general review of the literature on the subject including excellent case reports and complete bibliographies, I would recommend the articles by Campbell, Merrill, Outland and Clendening. Reports concerning specific portions of this material already have been published by two of my colleagues, Balfour and Lemon, and by Nadeau and MacCarty in a pathologic abstract.

The material comprising twenty-seven cases, all verified at operation, is composed of ten myomas, five fibromas, four angiomas, two dermoids, one gastric polyposis, two adenomas, and three polyps.

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Their histologic subdivisions will appear in the more detailed consideration of each group. These cases fall easily and logically into clinical classifications, a primary and a secondary; in the former group it was the presence of the tumor itself which caused the symptoms justifying surgical interference, while in the latter it was an associated or accidental finding during the course of an operation for another obviously major disease. A brief résumé of the entire series appears in Table 1.

The twenty-seven patients in the series were under observation in the Mayo Clinic between the years 1907 and 1921. During this period operation had been performed on 2,146 patients with cancer of the stomach, on twenty with sarcoma, and on two with malignant polyps of the stomach, a total of 2,168. The proportion, therefore, of malignant new growths to benign new growths is as seventy-eight to one, or 1.3 per cent of all gastric tumors were benign. But this proportion in our own experience is only relative, for during the same period 2,285 additional cases of malignant gastric neoplasms, the majority of them inoperable, passed through the Clinic.

Myomas.—This group, of ten cases, has been histologically subdivided into three leiomyomas, three adenoleiomyomas, and four fibromyomas. The three leiomyomas were classified clinically, primary. Two of the patients (Cases A19940 and A206857) were men aged sixty-six and forty-four respectively. Both had a marked myomatous hypertrophy involving more or less of the entire pyloric ring and presenting a palpable tumor, the first one 6 by 3 cm. in size. Both patients had distressing gastric disturbances over a long period in many respects simulating chronic ulcer. Hyperacidity and gross retention were present in the gastric contents of the former, and hyperacidity and hypersecretion in the latter. The third patient (Case A44684) was a male, aged forty-five, with symptoms extending over a period of five years. The type of tumor was unusual; the tumors were mural and multiple in the jejunum and esophagus ranging in size from 0.5 to 2 cm. with one of medium size in the pyloric antrum. This case was characterized by recurring melena, occasional diarrhea, dysphagia, and anemia, but an entire absence of dyspepsia.

The three adenoleiomyomas ranged in size from 1 to 2 cm., two were juxtapyloric on the greater curvature, the third on the anterior wall in the first portion of the antrum. Two were found during the course of an operation for ulcer or gallbladder disease.

The four fibromyomas are of considerable clinical importance since

three of them were primary, the patient seeking relief from them. The first patient was a man aged forty-eight, with a movable tumor above and to the right of the navel. His dyspepsia was of three years' duration, strongly simulating ulcer. Gastric analysis revealed moderate hyperacidity and food retention. At operation a fibromyoma 7 cm. in diameter on the posterior wall was removed. The second patient, a woman aged thirty-five, had had gastric complaint of three months' duration. The pain was usually severe. Gastric analysis and physical examination revealed normal conditions, but a filling defect of the pylorus, and a large barium residue was evident in the roentgenogram



FIG. 16.—Filling defect in the pylorus with a large six-hour retention. Small fibromyoma on the interior wall above the pylorus, close to the greater curvature.

(Fig. 16). At operation a small tumor 2 by 1 cm. was found on the anterior wall 4 cm. above the pylorus, close to the greater curvature. While the tumor was not pedunculated it could be manipulated as a ball valve, which probably explains the course of the painful seizures. The case of the third patient, a woman aged sixty-five, is one of the most interesting in the series. She had had distressing dyspepsia for six years, progressive in character, with intermittent periods of food retention provoking emesis, and a palpable movable, slowly growing mass in the left epigastrium of four years' duration. She had lost more than 60 pounds in weight during the two years preceding her

examination. For six weeks immediately prior to her admittance the patient had daily complained of irregular pains, of watery regurgitation and distress throughout the lower chest when swallowing and when regurgitating. Achylia and mucus were found on repeated gastric analysis, and a very unusual filling defect was revealed by the roentgenogram (Fig. 17). She had secondary anemia. At operation (C. H. Mayo) a fibromyoma 5 cm. in diameter was found on the posterior middle wall of the stomach 7.5 cm. above the pylorus. The tumor, dragging with it the posterior wall of the stomach, had invaginated through the pylorus into the duodenum a total distance of 12.5 cm., forming an



FIG. 17.—Unusual filling defect. Intussusception of the tumor with the posterior gastric wall into the duodenum.

intussusception of a portion of the stomach into the duodenum. Wade and Collier have reported similar complications in benign new growths. In addition to these the museum contains three specimens of fair-sized myomas which have undergone sarcomatous degeneration.

Fibromas.—The five tumors in this group occurred in patients ranging in age from sixteen to sixty-six. In one case, that of a small pedunculated fibroma, 7 by 2 mm., associated with a duodenal ulcer, the surgical records did not state the location, but the location in the remainder which were sessile was definitely pyloric. According to the literature, this situation is the rule, although our specimens neither



FIG. 18.—Prepyloric filling defect. Fibroma at the pylorus. Six-hour barium retention



FIG. 19.—Lesion at the outlet; moderate six-hour retention. Small fibroma of the anterior wall and pylorus.

showed malignant changes nor represented fibrous growths at the site of old ulcers. Tumors varied in size from that of the smallest, already mentioned, to a diameter of 2.5 cm. Because of the position of the

growth the roentgenogram revealed a filling defect in the pylorus and six-hour barium retentions (Figs. 18 and 19, Cases A208743 and A313898). In one patient (Case A53373), a woman aged forty, symptoms of two years' standing, continuous and progressively more marked for the last five months, in conjunction with anacidity, retained food masses, palpable tumor and a pyloric filling defect, certainly justified the diagnosis of gastric cancer. In a second case a fibroma, measuring 8 cm. by 5 mm. which involved the pyloric ring, presented a syndrome characteristic of duodenal ulcer of four years' standing with hyperacidity. A pylorectomy in this instance resulted in complete cure.



FIG. 20.—Large filling defect of the pars media and the anterior wall. Angioma of the stomach (6 by 5 by 5 cm.).

Angiomas.—The four tumors of this group are histologically hemangiomas. They are exceedingly interesting because of their size and rarity. Lemon reported the first one of the series in 1920 and up to that time only five others had been reported in the literature. Two of our patients, both women, were in the second decade of life, one in the fifth, and one in the sixth decade. With one exception free hydrochloric acid was present in normal amount and motility in all was unimpaired. With one exception the tumors were round, sessile, quite mobile at operation, of fair size, but not palpable on abdominal examination. They lay between the mucosa and serosa, were of soft



FIG. 21.—Angioma of the stomach as it presented on the mucous surface.



FIG. 22.—Filling defect on the posterior wall and greater curvature. Angioma on the greater curvature (2.5 by 2.5 by 2 cm.).

consistency, and bluish black or red; the one heretofore reported, situated in the fundus and anterior wall, suggested on palpation a mass of angle worms and the cut section resembled lung tissue (Figs.

20 and 21). In the second case the rounded pedunculated growth 2.5 by 2.5 by 2 cm., was attached midway to the greater curvature and posterior wall (Fig. 22). The ulcer crater in the apex of the tumor explained the bleeding and anemia. In the third instance an unusual bologna-shaped tumor measuring 11 by 3 by 2.5 cm., situated in the anterior wall was found. Dyspnea and weakness were the complaints presented, but on closer questioning an occasional sense of fullness after meals and emesis were revealed. The patient, a man aged fifty, was very anemic (hemoglobin 44 per cent), gastric analysis



FIG. 23.—Roentgenogram of tumor of the anterior wall of the stomach.

showed an absence of free hydrochloric acid, a considerable number of fresh red blood cells, and bits of tissue in the lower power field. These features, with the filling defect in the roentgenograms (Figs. 23 and 24), strongly suggested cancer, and this was made the provisional clinical diagnosis. The feces contained besides the blood, pathogenic amebas, and flagellates. The latter had probably provoked the diarrhea. Erosion was found in the tip of the growth.* The last case, the only one of its kind to my knowledge, illustrates the diagnostic value of routine roentgen-ray examination in all doubtful or obscure cases.

* A detailed description of the above four cases of hemangioma will appear in a paper by Dr. E. S. Judd.

The patient, a woman aged twenty-two, was of a nervous temperament, and had had dyspepsia since childhood which was characterized by nausea and marked frontal headache, occasionally extending to the occiput, usually appearing two or three hours after a meal, and terminating in an hour or two by vomiting of sour gastric contents,



FIG. 24.—Sausage-shaped tumor (11 by 3 by 2.5 cm.).

followed by complete relief. These attacks were brief and intermittent, were often provoked by dietetic indiscretions, and in later years were prevented by small amounts of soda before and after meals. Up to within six weeks before her examination epigastric distress or pain had been absent, but since that time she had experienced two violent

attacks of pain in the epigastrium about four hours after a meal, preceded by the usual dyspeptic symptoms and terminating in emesis with relief. The patient attributed these seizures to excitement of moving in the first instance, and in the second to the hasty preparation for a trip. The physical examination was practically negative, except for moderate anemia which was attributed to a severe menorrhagia present since the onset of menstruation at fourteen. She was 12 pounds below normal weight. Gastric analysis revealed normal acid values with hypersecretion. The roentgenogram (Figs. 25 and 26) revealed a large rounded, mobile mass in a dilated duodenum which was diag-



FIG. 25.—Large, rounded, mobile mass in a dilated duodenum.

nosed benign tumor. At operation (E. S. Judd) a rounded sessile mass just without the pyloric ring about 7 by 5 cm., covered by a thin mucosa, was easily removed. It had the gross appearance and feel of edematous myoma, but on section and microscopic examination it proved to be a hemangioma. The patient is having an uneventful convalescence. The painful seizures can best be explained by a temporary occlusion of the pylorus by the tumor.

Dermoids.—So far as I know only a few of these cases have been reported. Our first patient, a man aged thirty-one, was one of the earliest cases in the Clinic. For four years he had had recurring

attacks of hematemesis and melena finally causing severe anemia and weakness. Free hydrochloric acid was present (hemoglobin 40 per cent). A tentative diagnosis of asymptomatic, bleeding peptic ulcer was made. Operation revealed a rounded tumor of the posterior wall of the stomach 7 by 6 by 5 cm. This was diagnosed dermoid by the pathologist. The second patient was a boy aged eight. About four years previously his parents had noticed a small lump in his

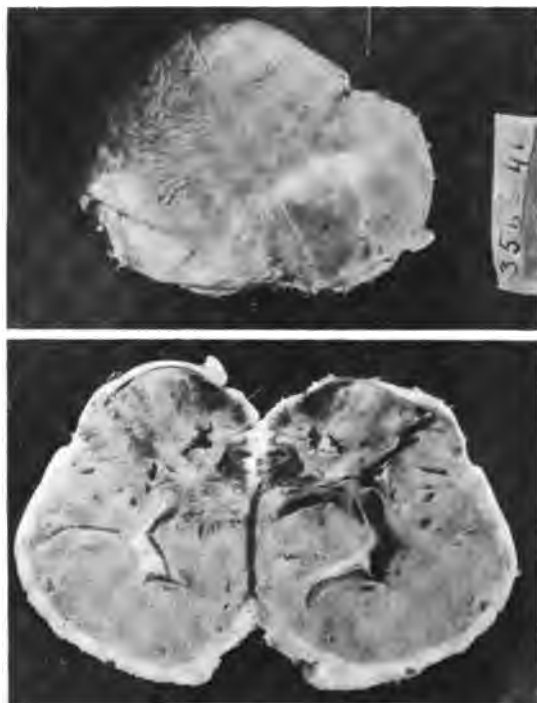


FIG. 26.—Photograph of angioma (7 by 5 cm.) removed from duodenum proximal to the pyloric sphincter.

abdomen, which seemed to be more prominent at times, especially when standing. The lump had enlarged gradually, but during the six months prior to examination growth had been marked. Aside from some urinary frequency the patient had no symptoms. Examination showed a large movable nonsensitive mass filling the upper and central portion of the abdomen. A gastric analysis was not made. Roentgenograms did not reveal retention from the six-hour barium meal. The stomach was very high, occupying a transverse position.

The placement upward was due to a large palpable tumor which was extrinsic and did not deform the gastric lumen (Fig. 27). At operation a gourd-shaped tumor, weighing 1,000 gm. was found attached to the posterior wall of the stomach and projecting into the lesser peritoneal cavity. The tumor was larger than the stomach itself. This was diagnosed dermoid cyst by the pathologist (Fig. 28).

Gastric polyposis.—This is probably the rarest form of benign tumor of the stomach. The only case seen in this Clinic has been described



FIG. 27.—Stomach displaced upward, occupying a transverse position.

in detail by Balfour. He states that the tumor was then found for the first time out of approximately 69,000 abdominal operations, 8,000 of which were for gastric lesions. Carman has seen only two cases in about 50,000 roentgen-ray examinations of the stomach, one of which was the one described by Balfour; the other was the case of polyposis reported by Myer. As a result of Myer's own careful clinical observations over a long period in this case, and of similar observations made in the cases of Wegele and Chosrojeff, he states that gastric polyposis

is more than probably present when such a combination of acute gastric hemorrhage, achylia gastrica, increased gastric motility and abnormal



FIG. 28.—Dermoid cyst (weight 1,000 gm.) of the posterior wall of the stomach in a boy aged eight.



FIG. 29.—Roentgenogram of gastric polyposis.

mucus production of an egg-white character is observed. Achylia gastrica, hypermotility, and excess of mucus were present in our case, that of a man aged thirty-one, with distressing epigastric symptoms

of eight years' duration. The roentgenograms in both cases are quite characteristic and show a diffuse mottled appearance of the pars



FIG. 30.—Appearance in the roentgenogram of the stomach after Pólya resection.



FIG. 31.—Gross specimen showing gastric mucosa studded with polyps.

pylorica and the lower pars media without six-hour retention or a corresponding palpable mass. This mottling is due to the displacement

of the barium by the approximation of the polyps which, offering no resistance to the roentgen ray, produce numerous small, black shadows in the silhouette of the stomach (Figs. 29, 30, and 31). Ruggles has recently reported one case with detailed roentgenologic findings. This tumor was described as a papillomatous rather than an adenomatous structure, as originally described by Menetrier. Finney and Friedenwald reported two cases of gastric polyposis which had undergone malignant degeneration.

Adenomas.—There were two of these tumors in the series, both were small and in women aged twenty-seven and thirty respectively. The first tumor, 2.5 by 1 cm., was situated 1 cm. above the pylorus and was a Brunnerian adenoma, first described by Hayem. It was mural, apparently symptomless and was excised during the course of an operation for gallbladder disease. The second one, found during the course of an exploratory operation, was also symptomless and was a small, hard inflammatory adenoma, 5 cm. above the pylorus on the lesser curvature. Novak and Stretton have recently reported single pedunculated adenomas on the posterior wall of the stomach, near the pylorus, in adults, causing symptoms simulating those of gallstone colic. The literature dealing with the various types of gastric adenomas has become fairly extensive.

Polyps.—The term polyp in the clinical or descriptive sense signifies any small pedunculated tumor. The majority of polyps are undoubtedly mucous. We have restricted the use of the term to adenomatous or papillomatous growths in conformity with pathologic terminology. There were three of these in the series. All the patients were women. The tumors had been found during operation for other major conditions. Two of the polyps were adenomatous, both single, one small, near the pylorus, the other 11 by 8 mm. on the posterior wall, 7.5 to 10 cm. above the pylorus. In a third case, that of a woman aged thirty-eight, the polyps comprised multiple papillomas, scattered throughout the stomach and jejunum, and varied in size from 5 mm. to 3 cm. This patient had a chronic duodenal ulcer.

SUMMARY AND CONCLUSIONS

The twenty-seven cases of benign tumors verified at operation, comprise seven different varieties in which are included myomas, with their histologic subdivisions, fibromas, hemangiomas, dermoids, polyps, adenomas, and so forth. They represent 1.3 per cent of all the gastric

tumors operated on. Seventeen of the entire number were clinically classified primary growths because they were found to be the chief cause of the patient's complaint. Perhaps the most interesting group in this series, because of comparative rarity and size, is that of the hemangiomas. Twelve of the patients with this condition were males and fifteen were females. The ages varied from that of a boy of eight with a 1,000 gm. dermoid on the posterior wall of the stomach, to that of a man of sixty-seven with a large hemangioma on the anterior wall and body of the stomach. The largest number, seven in each, was found in the second and sixth decades of life. One-half of all the patients were more than forty years. In thirteen cases the tumors were in close proximity to the pylorus, in five they occupied the posterior wall, in five the anterior wall, and in two they were generally distributed throughout the stomach. In one case in which the esophagus and jejunum were involved, and in another, an early case, the records do not state the exact location. The size and shape of the tumor were variable because of the various types encountered. The majority were sessile rather than pedunculated. Gastric analysis and symptomatology afforded little aid in the diagnosis. Practically all the smaller tumors were symptomless. Seven patients had palpable tumors, three of which were fibromyomas, three were fibromas, one was a dermoid, and one a leiomyoma. The average loss of weight in the primary group was 25 pounds. Ten patients had recurring hemorrhage with anemia and weakness. This was chiefly due to ulceration or erosion of a portion of the tumor. Three of the four patients with angioma had severe bleeding and anemia. Seven patients had obstruction, this includes one patient with a fibromyoma of the posterior wall which had caused an intussusception of the posterior wall of the stomach into the duodenum. Severe, painful seizures simulating gallstone colic were noted in several cases of juxtapyloric tumors which even though not pedunculated could be manipulated as ball-valve tumors. Myomatous tumors of the pylorus with or without pyloric obstruction simulate the duodenal ulcer syndrome. The roentgenologic appearance of the larger tumors is quite indistinguishable from that of gastric cancer.

Carman believes that a larger experience with this group will enable him to differentiate roentgenologically the two types more frequently than has been possible heretofore.

1. Benign tumors of the stomach are rare and constitute only 1.3

TABLE 1
BENIGN TUMORS OF THE STOMACH

Case.	Sex.	Age.	Lesion.	A. Location; B. Size.	Clinical features.
*A19940	M.	66	Leiomyoma.	A. Two-thirds of pyloric ring. B. 5 by 7 cm.	Gastric disturbances, irregular type; indefinite colic pains; later ulcer type; palpable mass in epigastrium; hyperacidity, gastric retention.
*A44684	M.	45	Leiomyoma.	A. Antrum, near pylorus, cardia and esophagus, jejunal. B. 0.5 to 2 cm.	Recurring melena, occasional diarrhea; dysphagia. Anemia; diagnosed asymptomatic bleeding ulcer. Gastric analysis not made.
*A206857	M.	40	Leiomyoma.	A. Pyloric ring. B. Well-marked muscle tumor.	In many respects had a duodenal ulcer syndrome. Hyperacidity and hypersecretion.
A891	M.	62	Adenoleiomyoma.	A. Greater curvature just above pylorus. B. 1.5 cm. in diameter.	Large ulcer on the lesser curvature with crater.
A77451	F.	60	Adenoleiomyoma.	A. Anterior wall of greater curvature 5 cm. from pylorus. B. 1 by 2.5 cm.	Cholecystectomy; appendectomy.
A209971	F.	28	Adenoleiomyoma.	A. Lower anterior wall. B. 1.5 by 2 cm.	Gastric neurosis.
*A40886	M.	48	Fibromyoma.	A. Posterior wall. B. 6 by 8 cm.	Three-year ulcer type of complaint; melena; high normal gastric acidity; obstruction; tumor.
*A142665	F.	65	Fibromyoma.	A. 7.5 cm. above pylorus; posterior middle wall. B. 5 by 7 cm.	Chronic painful epigastric complaint; achylia; movable, nodular tumor in left epigastrium; secondary anemia. Intussusception tumor with posterior gastric wall into duodenum (Fig. 17).
*A236057	F.	35	Fibromyoma.	A. Anterior wall 3.5 cm. above pylorus and close to greater curvature. B. 2 by 1 cm.	Gastric disturbance of three months' duration. Severe attacks of pain. Tumor near pylorus "ball-valve." Roentgen ray: filling defect in pylorus with large six-hour retention (Fig. 16). Normal acidity.

* Primary cause for operation.

A334803	F.	61	Fibro- myoma.	A. Anterior wall. B. 2.5 cm. in diameter.	Pelvic inflammation; chronic cholelithiasis; diabetes mel- litus.
*A53373	F.	40	Fibroma.	A. Submucosa; pylorus. B. 3.5 by 2.5 cm.	Indefinite dyspepsia for two years, continuous for last five months. Discomfort one-half hour after meals; emesis gave relief; subacidity; mobile tumor.
*A86627	M.	36	Fibroma.	A. Pylorus. B. 8 by 5 cm.	History similar to that of duodenal ulcer of four years' duration. Hyperacidity; occult blood in feces.
*A208743	F.	16	Fibroma.	A. Pylorus. B. 3 by 2.5 by 2.5 cm.	Ulcer type of complaint and associated with duodenal ulcer; secondary anemia. Palpable mass in the right epigastrium. Prepyloric filling defect (Fig. 18).
A241305	F.	51	Fibroma.	A. Not stated. B. Pedunculated; 7 by 2 mm.	Duodenal ulcer.
*A313898	M.	66	Fibroma.	A. Anterior wall. B. 1.5 cm.	Associated carcinoma of cecum; gastric history symptom- less; roentgen ray showed lesions at outlet; moderate six-hour retention (Fig. 19).
*A258233	M.	67	Hemangio- ma.	A. Anterior wall; body of stomach. B. 6 by 5 by 5 cm.	Complaint six months' duration; diarrhea; melena; two months' indefinite aching in left costal margin; two weeks' indefinite pain in right costal margin; sense of fullness with discomfort; appetite good; weight loss 25 pounds; free hydrochloric acid (Figs. 20 and 21).
*A324147	F.	25	Hemangio- ma.	A. Midway on greater curvature. B. 2.5 by 2.5 by 2 cm.	Atypical history; hematemesis, melena and diarrhea; anemia; normal gastric chemism; ulcer crater in apex of tumor; roentgen ray showed lesions in posterior wall and greater curvature (Fig. 22).
*A343572	M.	50	Hemangio- ma.	A. Anterior wall—bologna shape. B. 11 by 3 by 2.5 cm.	Dyspnea, weakness, severe anemia; no gross bleeding; occasional emesis and sense of fullness after meals. Ulcer area 3 cm. by 5 cm. on tip of tumor (Figs. 23 and 24).
* Primary cause for operation.					

BENIGN TUMORS OF THE STOMACH (Continued).

Case.	Sex.	Age.	Lesion.	A. Location; B. Size.	Clinical features.
*A356641	F.	22	Hemangioma.	A. Duodenopyloric. B. 7 by 5 cm.	Dyspepsia since childhood, provoked by indiscretion; nausea and headache two to three hours after meals, sour emesis and relief; prevented by using soda before and after meals. Two acute attacks of epigastric pain six weeks prior to admission (Figs. 25 and 26).
*Pl. 6206	M.	31	Dermoid.	A. Posterior wall. B. 7 by 6 by 5 cm.	Recurring hematemesis and melena; weakness; anemia (hemoglobin 40 per cent); no dyspepsia; free hydrochloric acid present.
*A136147	M.	8	Dermoid.	A. Posterior wall. B. 1000 gm.	Upper abdominal tumor of gradual growth, of four years' duration; increased markedly in size in last six months; urinary frequency (Figs. 27 and 28).
*A250518	M.	31	Polyposis.	A. Entire lower two-thirds of stomach.	Indigestion for eight years; ulcer type of complaint continuous for past year; no nausea or vomiting; occasional diarrhea; no hemorrhage; loss of weight; achylia; mucus; characteristic roentgen-ray findings (Figs. 29, 30, and 31).
A237007	F.	27	Adenoma (Brunnerian).	A. 1 cm. above pylorus. B. 2.5 by 1.5 cm.	Gallbladder disease.
A2206	F.	30	Adenoma.	A. Lesser curvature 5 cm. above pylorus.	Gastric neurosis; chronic appendicitis.
A80723	F.	29	Polyp (adenoma).	A. Near the pylorus. B. "Small."	Gastric resection for hypertrophy of the pylorus.
A220699	F.	20	Polyp (multiple papillomas).	A. Throughout stomach and jejunum. B. 5 mm. to 3 cm.	Duodenal ulcer; second operation later for resection of jejunum.
A343402	F.	38	Polyp (adenoma).	A. Posterior wall 7 cm. to 10 cm. above pylorus. B. 11 by 8 mm.	Gallbladder disease; migraine; anemia; healed tuberculosis at both apices.

* Primary cause for operation.

per cent of all gastric tumors that have come to operation. The actual proportion of benign new growths to malignant new growths or ulcerations is as 1 is to 200.

2. Myomas and fibromas constitute the largest group, gastric polyposis the most infrequent.

3. About 50 per cent of benign tumors are found in patients more than forty. There is no characteristic syndrome and gastric chemism ranges from achylia to hyperacidity with hypersecretion. The summation of evidence favors the diagnosis of gastric cancer.

4. The majority of the tumors are situated in the region of the pylorus, the greater curvature, anterior and posterior walls.

5. The smaller tumors are practically symptomless unless situated at the orifices, or unless multiple.

6. Common complications are recurring hemorrhage, which occurred in 37 per cent, and pyloric obstruction which occurred in 25 per cent. Palpable mass, food retention, or six-hour barium retention is less frequent than in gastric cancer.

7. Often patients with benign gastric tumors are refused operation because the condition is regarded as malignant and inoperable. The true nature of the lesion is discovered only when the patients insist on operation.

8. The surgical end results are excellent.

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DIAGNOSTIC AND THERAPEUTIC ASPECTS OF LATE SEQUELÆ OF GASTRIC SURGERY: OBSERVATIONS BASED ON 6400 OPERA- TIONS FOR CHRONIC GASTRIC AND DUODENAL ULCERS*

GEORGE B. EUSTERMAN

This article embodies, in the main, my experience and opinion with regard to factors contributing to the failure or success of the surgical treatment of patients with chronic benign ulcer of the stomach or of the duodenum. The subject was chosen partly because of a growing suspicion of physicians regarding the ultimate benefits derived from purely surgical interference, especially following gastro-enterostomy for uncomplicated juxtapyloric lesions, and partly in view of the diagnostic problems and therapeutic considerations arising as the result of late sequelæ.

A full consideration will not be given of the relative merits or indications for medical and surgical treatment; of the antagonistic views held by prominent internists with reference to the virtue of purely medical measures, or of the uncompromising attitude and the occasion for it of the majority of surgeons regarding nonsurgical therapeutics. It seems that these and numerous other causes for disagreement lie largely in the fact that our present knowledge concerning many fundamental factors of normal and morbid gastric physiology, and of the lesion itself, is incomplete. Besides there is an absence of uniform standards of selection, judgment, and skill in the management of ulcer bearing patients. To those intimate with the difficulties of our problem there is a feeling that we are passing through a transitional stage so far as the treatment of ulcer is concerned. While we appreciate the limitations of medical treatment there has also been a growing dissatisfaction among surgeons with the results of their treat-

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ment. A study such as this wherein we may see the factors that made not only for failure, but also for success in the past may perhaps serve the added purpose of evaluating any change or addition to our future therapeutic armamentarium.

Inasmuch as about 70 per cent of all ulcers are duodenal, and about 65 per cent of all gastric ulcers are at or near the pylorus and on the lesser curvature, posterior gastrojejunostomy, with or without cauterization or knife excision, has been the usual operative procedure in the Mayo Clinic. Therefore my observations and statistical review deal chiefly with this large group. In the discussion that follows bearing on the causes for failure or incomplete relief after operation the fact should not be lost sight of that in our experience, as statistics will show, the end-results have been highly favorable. Failures after medical treatment are taken as a matter of fact, but failures after operation are often given undue prominence, a psychologic fact of considerable importance.

Immediate postoperative complications, while they may have an important bearing on later sequelæ, do not come within the province of this paper. Patients under observation following unsuccessful surgical treatment may present a variety of symptoms, chiefly pain or distress, emesis, hemorrhage, and intestinal disturbances. The underlying causes may be purely neurotic, or they may be due to functional derangement or to gross lesions. Moynihan, whose experience has been very similar to that in the Clinic, gives the following as the chief reasons for failure:

1. The performance of gastro-enterostomy in the absence of a lesion intrinsic to the stomach or duodenum.
2. Faulty technic, which often gives rise to the symptoms of vicious circle, the result of obstruction of one of the jejunal limbs, especially the distal one, or the result of too small a stoma or too long a jejunal loop.
3. Lack of thoroughness in operating, such as neglecting to remove a diseased gallbladder or an appendix at the time of an otherwise successful operation, or to deal directly with an ulcer-bearing area when circumstances warrant it.
4. Formation of a new ulcer in the stomach or duodenum, at or beyond the stoma, and reactivation of the partially healed or unhealed ulcer, or carcinomatous changes in a gastric ulcer not removed at the primary operation. In these cases such sequelæ give rise essentially

to painful symptoms at variable periods after operation in which the complaint is often identical to the original. Similar distress may be provoked by extensive adhesions at the pylorus or by those involving the stomach and anterior abdominal wall, the result of repeated operations or undue manipulations.

The patients who have come under our observation may be divided roughly into two groups:

Group 1.—Almost all of the patients in the first group had been operated on primarily elsewhere and the causes of their recurring symptoms were usually due to (1) operation in the absence of a lesion, a technical error, or to a combination of both (about 200 gastro-enterostomies have been undone by surgeons in the Clinic which include a number of their own) or to (2) gastrojejunal or jejunal ulcer. Secondary operations for the removal of such lesions were performed in forty-four cases; these complications are more serious than the original lesion. In about one-third of these cases there was no tangible evidence of a preëxisting lesion.

The group of patients with recurring symptoms who had been operated on elsewhere represents the most difficult problem in diagnosis because of (1) invariable absence of authentic data concerning the operative findings, the details of operative procedure, and the degree of technical skill; (2) the possibility of the recurring symptoms being due to the original causes underlying the complaint, often nervous or reflex, especially in the absence of reliable preoperative clinical evidence for ulcer; (3) the roentgen-ray determination of postoperative complications made difficult because of the inevitable physical and functional changes incident to operative intervention (Carman); and (4) subjective cures being found when laboratory examinations indicate a disturbed physiology, and the appearance of postoperative symptoms when the functions seem to be improving, or when they are within normal limits (Wilensky). But if the postoperative state of the patient is worse than the preoperative, or, as is often the case, the postoperative symptoms are different and more urgent, common sense dictates secondary surgical intervention since the complication is invariably of a mechanical nature.

Group 2.—The patients in this group had demonstrable lesions of the gastroduodenal area which were found and corrected. Other lesions of the accessory digestive tract when present and amenable to surgical interference were removed by the surgeons.

SEQUELÆ DEMANDING SECONDARY OPERATIONS

In our cases failure to achieve cures made 228 secondary operations necessary out of a total of 6,402 operations of all types for chronic benign ulcer; there were 4,793 posterior gastrojejunostomies alone. The causes underlying the recurrence or continuation of painful symptoms have been mentioned. Reliable statistical data are not available with regard to the frequency of reactivated ulcer. It is reasonable to infer that the resumption of the original symptoms of variable severity when associated with hyperacid gastric secretion and responding favorably to proper and adequate medical measures are due to this factor. Especially is this true in the persistent absence of any definite clinical or roentgenologic evidence of a new ulcerative process.

Gastrojejunal or jejunal ulcer necessitated secondary operations in fifty-seven cases. Such sequelæ are undoubtedly more frequent because in some instances the disturbance from the ulcer may not be sufficient to bring the patient back for treatment, or he may seek treatment elsewhere. In at least ten additional cases a conclusive diagnosis of such a lesion was made; four of these patients submitted to an intensive medical régime.

OTHER CLINICAL AND DIAGNOSTIC DATA

Wright has called attention to the preponderance of the male sex in cases of gastrojejunal and jejunal ulcer. Forty-nine of our fifty-seven patients were males and eight were females. In more than half the patients the pain was left-sided and lower than before the operation. Eighty-eight per cent of the patients, including those who experienced no relief from the operation, had a recurrence of symptoms within one year following the operation. Other data of clinical interest and diagnostic importance have been emphasized in my study of eighty-three proved cases.⁶ An accumulative experience has enabled my colleagues in roentgenology to detect the lesion with surprising frequency.

Judd has recently reported the entire series of 101 cases of gastrojejunal ulcers observed at the Clinic. In these cases eight of the lesions were distinctly jejunal in location.

The formation of a new ulcer at or near the site of the original ulcer was the occasion for a secondary operation in twenty-one patients. This occurrence is exclusive of the gastrojejunal group in which reacti-

vation of the primary ulcer or the formation of a new ulcer was not uncommon. Again the male sex predominated, as only four of the patients were females. The period of relief following the first operation ranged from three months to eleven years, but 70 per cent of the group had a recurrence of symptoms within an average period of one year and eight months. Three patients had no relief whatever. Twelve of the recurring ulcers were gastric; in seven the original ulcer was gastric and, with one exception, excision alone, pyloroplasty, or sleeve resection was performed originally. In the remaining five cases there were concurrent lesions originally in the stomach and duodenum, and gastro-enterostomy with or without excision of the gastric ulcer was the original operation. In the nine instances of a new duodenal ulcer the original lesion was in the duodenum, and the primary operation in seven was excision, plastic operation, or simple enfolding. In the remaining two a posterior gastrojejunostomy had been performed. The few new gastric ulcers that had apparently developed in the presence of a gastro-enterostomy admit of much speculation. The majority of recurring ulcers, of course, followed excision or pyloroplasty.

Carcinoma developing on benign gastric ulcer for which a previous gastro-enterostomy alone had been performed was found at secondary operation in twenty-three cases. This group represents an earlier series, for in more recent years the Balfour cautery or knife excision combined with gastro-enterostomy, pyloroplasty, or some form of resection is the routine procedure. In ten more recent instances, however, operation revealed carcinoma developing at or near the site of a former gastric ulcer in which surgical measures other than gastro-enterostomy were instituted originally.

In a total of 144 of 4,793 gastro-enterostomies, or in 3 per cent, for miscellaneous reasons besides those enumerated, a secondary operation was performed. In the remaining eighty-four a secondary operation was undertaken chiefly because of complications developing after excision or pyloroplasties for gastric ulcer, but the proportion of such primary operations to gastro-enterostomies was much smaller.

Graham, in 1914, reported the surgical end-results in 600 cases of duodenal and gastric ulcers. There were 438 patients with duodenal ulcer and 94 per cent of 163 of these who had pyloric obstruction of variable degree at the time of operation were cured. Of the entire group 88 per cent were cured or satisfactorily improved. Since that time answers to questionnaires from 1,800 additional patients have

been tabulated. The percentage of patients cured or greatly improved remains approximately the same in the two groups. As Balfour has shown, the added routine procedure of cautery or knife excision, especially the former, has, among other procedures, almost nullified the possibility of postoperative hemorrhage, and the percentage of patients classified as improved has been much increased. In order to maintain these percentages the surgeon must continue to be conservative in accepting the young male adult with active gastric chemism and the psychoneurotic ulcer-bearing patient, if intensive medical management can be the alternative. Deaver has recently reported a cure in 90 per cent following operation for duodenal ulcer.

ADVANTAGES OF GASTRO-ENTEROSTOMY OVER PYLOROPLASTY

In view of such favorable end-results by almost purely surgical procedures and the fact that a secondary operation was necessary in only 228 cases of the 6,402, it is difficult to follow the logic of physicians who argue that gastro-enterostomy is inherently faulty. The average duration of symptoms in our ulcer-bearing patients was nine and one-half years, and such complicating factors as pyloric obstruction, recurring hemorrhage, and chronic perforation, singly or in combination, were present in 35 per cent. A leading American exponent of medical therapy in several personal communications has emphasized his conviction from repeated careful study that a properly performed gastro-enterostomy in the presence of a chronic indurated duodenal or pyloric ulcer is a splendid physiologic procedure. Total and free acidity in our cases is reduced from 40 to 60 per cent following gastro-enterostomy. As C. H. Mayo has said, this procedure permanently applies the principle of medical treatment, bringing about a change in the local environment, which invariably permits nature to heal the ulcer as well as to overcome symptoms. Carman, on repeated fluoroscopic examination at variable intervals after operation, has shown that (1) the stomach is usually smaller than before operation unless marked dilatation existed previously; (2) the stomach empties in considerably less time than the normal unoperated stomach; and (3) the opaque meal passes freely through the stoma, which does not tend to contract materially. Proponents of some form of pyloroplasty (Finney, Strauss, Horsley, and Davis) in preference to gastro-enterostomy have advanced some plausible arguments. The decision of the best type of operation is a problem

that the surgeons must solve although an expression of opinion from the clinician may not be out of place. My experience with the end-results of several hundred well executed pyloroplasties, many performed under favorable circumstances, has not been encouraging. Recurrence of ulceration in the suture line, adhesions to adjacent viscera, induration, contraction, and narrowing, which provoke faulty pyloric mechanism and serious functional disturbances in the absence of adequate obvious cause, are occasional sequelæ. My answer to the charge that gastro-enterostomy is an unphysiologic procedure is that at least 15 per cent of all pyloroplasties eventually prepare a rich soil for a highly successful gastro-enterostomy. Therefore it is reasonable to believe that time and an enlarged experience will temper the present laudable enthusiasm for pyloroplasty.

CONCLUSION

The nihilism with regard to therapeutics manifested by the surgeon in the past is not a flattering chapter in the annals of achievement in the domain of gastric surgery. In more recent years this attitude has changed, as evidenced in the contributions of representative surgeons, such as Mayo, Judd, Wilensky, and Davis. This attitude augurs well for surgery and for the patient. Medical management has been discredited, not because the principle is wrong, as the capacity for healing in ulcers is variable, but because the effort was inadequate and the coöperation of the patient was not sufficiently cultivated. Consistent medical management is often superior to poor surgery, and the mortality is practically nil. The prospect for cure following a successful operation has too frequently been forfeited through the gross dietetic indiscretions of the neglected patient. Many functional derangements of organs beside the stomach often of major importance, that surgery cannot be expected to cure, require the coöperation of the internist for their alleviation. Bastedo bluntly says that no longer shall we tolerate a surgeon who places a patient with an ulcer on a heavy and bulky diet within two or three weeks of his operation. All this emphasizes the necessity of friendly coöperation between the internist and the surgeon. Unquestionably, the best interests of the majority of ulcer-bearing patients are conserved by such combined efforts. In the Mayo Clinic the surgeons leave to the clinicians the preoperative preparation and the details of the immediate and later postoperative dietetics, alkaline therapy, removal of foci of infection, and regulation of the future life

of the patient. It seems safe to predict that the pooling of all therapeutic resources will prevail over the present tendency of surgeons to institute newer or more radical measures in surgical technic for the cure or alleviation of a widely prevalent and increasing disease.

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STUDIES OF THE CAUSE OF PAIN IN GASTRIC AND DUODENAL ULCERS. STUDY II. PERISTALSIS AS THE DIRECT CAUSE OF PAIN IN GASTRIC ULCERS WITH ACHYLIA AND IN DUODENAL ULCERS*

LEO L. J. HARDT

For many years clinicians have been aware of the fact that not infrequently the symptoms of infection of the gallbladder and appendix, and of achylia gastrica of unknown etiology may simulate those of typical gastric or duodenal ulcer. Since reflex pain may be indistinguishable from the true pain in ulcer, to what should this gastric pain, brought on by extragastric lesions, be attributed? Is there direct damage to the stomach and duodenum through this reflex mechanism?

In the consideration of the cause of gastric pain from gastric and duodenal ulcers or reflexly from an infected gallbladder, appendix, or achylia gastrica, two factors are of importance. On the one hand is the question of acidity or hyperacidity and hypersecretion, and, on the other hand, variations in tonicity, intragastric tension, and peristalsis of the stomach and duodenum. Clinicians generally have been satisfied with the plausible explanation of hyperacidity and hypersecretion as the most likely cause of pain; as proof of their statement they administer alkali which stops the pain, and quite logically they conclude that control of the pain and subsequent healing of the ulcer are mainly questions of neutralization. This view has been substantiated by Cannon in his classical work on the acid control of the pylorus. His theory does not explain the emptying of the stomach in gastric achylia, the rapid exit of water and egg albumin, nor the observations of Spencer, Meyer, Rehfuess, and Hawk, that a 1 per cent solution of sodium bicarbonate hastens the discharge from the normal human stomach.

The experimental work of Luckhardt, Phillip, and Carlson indicates very conclusively that the pylorus opens for the ejection of chyme when

* Reprinted from the Archives of Internal Medicine, 1922.

it is reached by powerful advancing rings of contractions and when tonicity of the stomach musculature is greatly increased. The gastric contents entering the duodenum are usually acid to phenolphthalein, but rarely show the presence of free acid to dimethylamidoazobenzaldehyd.

Carlson, Ginsburg, Tumpowsky and Hamburger, and Hardt, working independently, have demonstrated, by means of kymographic records, various types of contractions and peristalsis of the stomach, which they concluded are the main factors in the causation of the pain of ulcer. New light was thrown on the etiology of pain not only from gastric or duodenal ulcers, but also from achylia gastrica.

INVESTIGATION

Method.—The relation of gastric motility to pain was studied in twenty-five patients by the kymographic method. All patients were given a standard meal, consisting of two soft boiled eggs, two pieces of toast, two glasses of milk, and the juice of a grapefruit. One to two hours later two tubes were swallowed, a Rehfuß tube and a small rubber tube with a fine rubber balloon attached at one end and a chloroform manometer to the end which projected from the mouth. The balloon, held as close as possible to the cardiac end of the stomach, was blown full of air; it was compressed according to the various types of contractions of the stomach, and thus air forced into the manometer caused the rider to record the variations in tonicity and the contractions on a slowly moving kymograph. These tracings were continued for from one to three hours, and at intervals of one-half hour 15 to 30 c.c. of stomach contents was aspirated to determine the presence or absence and percentage of free and total acids. The twenty-five patients were divided into two groups:

Group 1.—This group comprises twenty patients with duodenal ulcers, the majority of whom came to the Clinic during a quiescent period in their trouble. The diagnosis was based on the clinical history and confirmed by roentgen-ray examination. All these patients were treated medically by the Sippy method at the completion of the kymographic record. None of the patients whose kymograph showed only Type I contractions (Fig. 32) experienced pain. All of these patients during the course of the experiment revealed adequate free acids ranging from 20 to 90 (in terms of one-tenth normal hydrochloric acid).

Six of the patients in whom contractions of Type III (Fig. 33) or Type IV (Fig. 34) were recorded, experienced burning or gnawing pain similar to pain in ulcer, in practically every instance synchronous with the



FIG. 32 (Case A147732).—Type I contraction. Tonus variation or digestive peristalsis, without pain.

peristalsis, but as long as Type I contractions were recorded they were without pain.

The degree of acidity seemed to have little bearing on the pain. The acidity on the whole was lower at the time of the pain and active peristalsis than during the absence of pain and slight peristalsis.

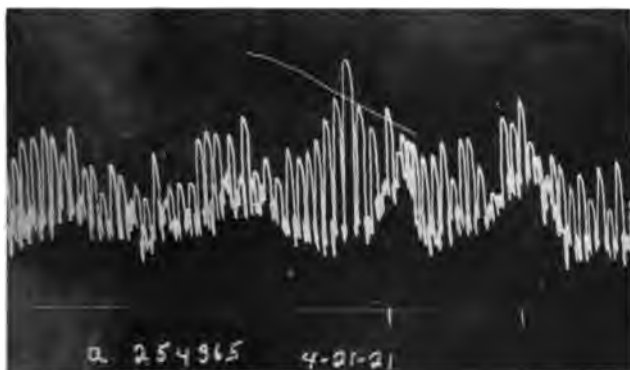


FIG. 33 (Case A254365).—Type II contraction. Exaggeration of tonus variation which precedes the vigorous peristalsis; frequently associated with a moderate amount of pain.

Group 2.—This group comprises five patients with achylia gastrica. Three patients were without pain and without any demonstrable pathologic condition, one patient had gastric ulcer and one had pain

without any demonstrable pathologic condition. The three patients without pain had no definite epigastric distress other than a little bloating or a burning sensation. Two of them revealed only Type I contractions during the course of the experiment; but the third had

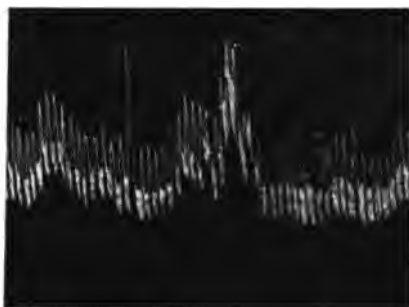


FIG. 34 (Case A351625).—Type III contraction. Beginning hunger peristalsis, with pain.

definite Type II (Fig. 33) and Type III peristalsis. These three patients clearly show that normal tonus variations and peristalsis can be present in achylia gastrica. The patient with gastric ulcer (Case A147732) had repeated gastric analyses which failed to reveal evidence of free acids. The typical epigastric pain of a gastric ulcer continued, pain coming

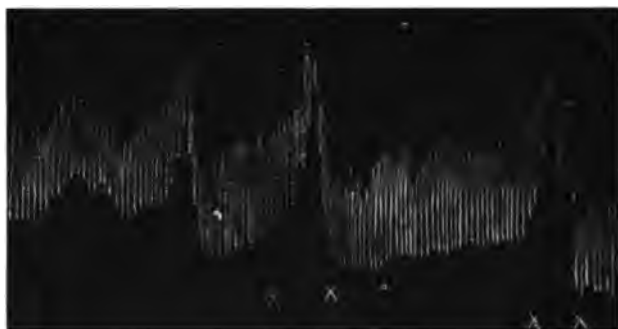


FIG. 35 (Case A356604).—Type IV contraction. Vigorous hunger peristalsis, which is coincident with gnawing or burning pain.

on from two to three hours after eating, with relief by food, water, alkalis, gastric lavage, and emesis. On several occasions during a period of distress, acid-free contents were washed out of the stomach and the patient obtained prompt relief. Kymographic tracings begun two hours after a test meal showed tonus variations without pain (Fig. 33); but

gradually as the tonus variations were replaced by more active contractions of Type II and Type IV intermittent epigastric pain was complained of, which in almost every instance was synchronous with the peristalsis. The fifth patient (Case A254365) had pain typical of ulcer, differing somewhat in that it continued for long periods without remission, but no demonstrable pathologic condition. Several analyses of gastric contents failed to reveal any evidence of free acidity. At the time the patient experienced pain the kymograph recorded Type II (Fig. 33) and Type III (Fig. 34) contractions, the pain being absent during the period of slight tonus variations (Fig. 32).

REPORT OF CASES

Case A147732. Mr. S. A. M., aged forty-nine years, first came to the Clinic December 11, 1915, complaining of epigastric pain three to four hours after meals. The attacks occurred in spells lasting for from a few weeks to a month and remissions lasted for from three to five months. Belching, drinking hot water, milk, or cream had usually given relief. For three months beginning August, 1915, he had vomited nearly every night between 1 and 3 a.m.

Operation, December 20, 1915, revealed a perforating duodenal ulcer extending into the pylorus, with adhesions to the head of the pancreas and with almost complete closure of the pylorus. Gastro-enterostomy and appendectomy were performed. Gastric analysis at this time revealed total acids 42 and free acids 30, with laboratory findings pointing to pyloric obstruction. The patient was free from symptoms for three months following operation.

From 1916 until the patient's second admission to the Clinic June 19, 1921, he had frequent attacks of epigastric pain two to three hours after meals, which were relieved by emesis, food, and alkalis. Roentgen-ray examination revealed a gastric ulcer.

At operation June 27, 1921, scar tissue was found on the duodenum, but no ulcer within. An ulcer 1.5 cm. in diameter was located on the lesser curvature of the stomach 3.75 cm. above the pylorus. The gastro-enterostomy was found to be patent and functioning. The ulcer was excised and the diagnosis confirmed by microscopic examination.

Case A254365. Mr. M. T., aged twenty-five years, first came to the Clinic December 26, 1918. He complained of epigastric distress of a burning character one hour after meals and at midnight. The pains were usually relieved by eating. In addition he complained of diarrhea which was closely associated with the epigastric distress. Gastric analysis failed to reveal any free acidity. *Endamoeba histolytica* was found in the stools. He was given emetin treatments for five days and sent home with advice as to treatment of diarrhea.

December 26, 1919, the patient returned, still complaining of frequent attacks of burning pain in the epigastrium. The pain would be present for three or four days and then disappear for a week. The diarrhea had cleared up. He was given bromids three times daily after meals.

December 27, 1920, the patient again returned with identical gastric complaints. The bromids had given relief for six months. This time he was given dilute hydrochloric acid, fifteen minutes after meals.

April 19, 1921, the patient returned with epigastric pain which had not been relieved by the previous treatment with hydrochloric acid.

The stomach had been examined with the roentgen ray on each admission, but no evidence of gastric or duodenal ulcer had been obtained. Repeated gastric analysis had failed to reveal any free acids.

At the last visit kymographic records were taken which showed that the pains were intermittent and coincident with the active peristalsis. Alkalis and tincture of belladonna gave relief.

COMMENT

The two groups of patients substantiate the theory of variations in tonicity and peristalsis as the main factor in the cause of gastric pain; the acidity is considered a secondary and in some cases not even a necessary finding, as in the two cases of achylia gastrica. That the motility and tonicity of the stomach is quite independent of the acidity is indicated by the cases of achylia in which all the normal contractions were obtained in the absence of acidity. Furthermore, emptying of the stomach was not interfered with, since in none of these cases was there the slightest symptoms or signs of retention.

The quiescent period is probably the result of a diminution in the degree and extent of the inflammatory process, together with a decrease in the tonicity and contraction of the gastric and duodenal musculature. The administration of food, alkalis, water, emesis, and gastric lavage temporarily produces this quiescent state, mainly through the inhibition of the peristalsis which is replaced by the nonpainful digestive peristalsis, described by Rogers and Hardt. The acid in all probability merely exaggerates to some extent the pain resulting from the more vigorous peristalsis and pyloroduodenal spasms.

The logical therapy in cases of gastric and duodenal ulcer should, it seems, tend primarily to inhibit peristalsis. About 85 per cent of the patients treated surgically in the Mayo Clinic have been cured of the ulcer or satisfactorily improved. It might be assumed from these results that surgical procedures inhibit the vigorous peristalsis for a period long enough to promote healing of the ulcer, or at least a subsidence of the more acute inflammatory process. It is hoped that in the future this assumption can be demonstrated more conclusively by the kymographic method.

CONCLUSIONS

1. Gastric ulcer may be present in patients with achylia and may produce all the clinical symptoms characteristic of ulcer. The pain is primarily due to the peristalsis acting on an irritable focus. All the

medical measures by which gastric acidity is neutralized and suppressed also inhibit the gastric peristalsis and thus relieve the pain.

2. Patients with gastric achylia in the absence of any demonstrable organic lesion may reveal the normal tonus variations and peristalsis.

3. Patients with uncomplicated duodenal ulcer do not experience pain during the period of digestive peristalsis, even in the presence of an adequate acidity. Active peristalsis of the "hunger type" (Types III and IV) is essential in the production of pain.

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CIRCUMSCRIBED SYPHILITIC ULCER OF THE STOMACH: REPORT OF A CASE*

GEORGE B. EUSTERMAN

The last of my three previous articles on the subject of gastric syphilis contained a summary of observations and conclusions based on a series of fifty-five cases. Since that time ten more cases have been added to the list. The case in this report represents an unusual type. A careful study of the material mentioned disclosed outstanding characteristics as follows:

1. Organic gastric syphilis is rare even in advanced stages of systemic syphilis. The average age incidence is between thirty-five and forty years, the average duration of symptoms about two years, and the average duration of the infection about twelve years. In contrast the average age of the patients with chronic benign calloused ulcer is forty-five years, with symptoms on an average of from nine to ten years; the patient with cancer averages fifty-four years, with symptoms of two and one-half years' duration. Exclusive of the patients with heredo-syphilis and the advanced obstructing hour-glass types, cachexia is rare, anemia is not marked, and invariably a gastric tumor is not palpable.

2. There is no symptomatology characteristic of the lesion, and variations in the clinical picture depend largely on the site and extent of the involvement. Localized involvement of the pylorus with or without stenosis and with free hydrochloric acid and enzymes in the gastric secretion may simulate benign pyloric ulcer; in cases of obstructing hour-glass, the patients usually have considerable pain, and vomiting soon after taking food; in the contracted and deformed types there is distress, pain, and symptoms in proportion to the nature and amount of the food taken. The symptoms in the main closely approach those characteristic of a slowly progressive form of scirrhus carcinoma. The symptoms common to all the cases were a fairly marked progressive course, pain soon after eating, invariably associated with nausea and

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vomiting, the absence of hemorrhage, maintenance of appetite in the majority of cases, and marked loss of weight without definite cachexia. Achylia was present in more than 80 per cent of the cases; in 20 per cent there was free hydrochloric acid in the gastric extract, but usually with subnormal values. In 7.5 per cent of the latter achylia alternated with free hydrochloric acid secretion.

3. The pathologic anatomic process in all the cases was a progressive inflammatory one, rarely circumscribed, and involved the lower and middle thirds of the stomach in the majority of cases, with extension upward along the lesser curvature. Hour-glass contractures usually involved the pars media. General diffuse syphilitic cirrhosis was characteristic of the congenital cases. In advanced cases hour-glass contraction, marked thickening, deformity, and contracture due to fibrosis was the rule.

4. In from 50 to 60 per cent of all cases of proved gastric carcinomas a tumor is palpable, in contrast to 15 per cent in the syphilitic cases. In proved cases of gastric carcinoma in all stages free hydrochloric acid is found in 46 per cent, but it is absent in 80 per cent of all cases of gastric syphilis.

5. Carman states that although the roentgen signs of gastric syphilis are not distinctive and pathognomonic in every case, they furnish decisive evidence of gastric involvement and in correlation with the clinical and laboratory findings give indispensable aid in the diagnosis of this disease. In his judgment the roentgenologic signs of gastric syphilis are: (a) filling defect of the gastric outline, usually without corresponding palpable mass, (b) hour-glass stomach (dumb-bell) or the upper loculus expanded and bulbous, and the lower loculus tubular, due to extensive irregular concentric contraction, (c) six-hour retention less frequent than in other gastric lesions (about 20 per cent), (d) diminution of gastric capacity, (e) stiffening or lessened pliability of the gastric wall, (f) absence of peristalsis from the involved area, (g) pylorus free rather than obstructed, (h) patient usually under cancer age and not ill in proportion to the extent of the disease shown by the roentgen ray, and (i) absence of a niche, accessory pocket, or typical incisura, classic signs of simple gastric ulcer.

6. Intensive syphilitic treatment in the early stages may produce actual clinical and anatomic cure. In advanced cases there may be little or no response. In the series of fifty-five cases previously reported a clinical cure was shown in 42 per cent and improvement in

50 per cent, representing a total of 92 per cent improved or cured. This includes twelve cases (30 per cent) in which anatomic restitution to normal was complete or nearly complete.

7. The proof of the specificity of a lesion involves numerous factors. The requisites are: demonstrable evidence of a gastric lesion, positive Wassermann reaction or other reliable evidence of syphilis elsewhere in the body, or both, and definite, sustained therapeutic improvement. These factors in conjunction with achylia or subacidity in the majority of cases, with the roentgenologic characteristics herein described, in addition to anatomic improvement or cure, seem to make the clinical or *intra vitam* diagnosis of syphilis of the stomach conclusive. The following is the composite picture of acquired gastric syphilis:

The patient is usually a male adult whose average age is thirty-five years. His gastric disturbance has been, on the average, of a little more than two years' duration, and characterized chiefly by pain, vomiting, and flatulency, coming on fairly promptly after meals. Little or no relief is experienced by ordinary methods of management. The clinical course is progressive. Gastric chemism and roentgen findings strongly suggest cancer. The patient is undernourished, but not cachectic, may be somewhat anemic, and usually an epigastric mass is not palpable. The gastric lesion is invariably extensive, occasionally localized in the pyloric area, with only a slight tendency to produce stenosis. Such characteristics in conjunction with a positive Wassermann reaction, or with a history of infection and other clinical signs of syphilis, are strong presumptive evidence of specific gastric disease.

REPORT OF CASE

Case A304048. Mr. W. H. H., aged forty-six years, farmer, was examined in the Clinic January 23, 1920. He had had gonorrhea in 1895, malaria in 1898, syphilis in 1900, rheumatic fever in 1903, and influenza in 1918. A local physician treated the primary lesion with calomel powder and it disappeared in a few days. The patient had no knowledge of skin or mucous membrane secondaries, alopecia, and so forth. About one year afterward he had paralysis of the left side of the face which lasted six months associated with "sore throat" for about one week at the outset. Potassium iodid was prescribed and taken for one and one-half years without untoward gastric symptoms. The patient had married in 1905. Two years after marriage abortion was induced (?) at two and one-half months. There were no further pregnancies and no precautionary measures were taken. The wife was given a divorce by publication eight years after marriage.

The patient had not had gastro-intestinal disturbances prior to October, 1919. At this time symptoms developed gradually, but became quite marked within six weeks. He complained chiefly of distress, sometimes a severe pain, chiefly localized to the anterior lower portion of the chest. This distress or pain usually appeared about thirty minutes

after meals and was associated with belching, never with actual nausea or vomiting. His appetite failed from the outset, and he was apprehensive on account of the proximity of the pains to the precordium. The pains were never epigastric. On occasions he regurgitated his partially digested breakfast at 6.00 p.m. with considerable relief from subjective discomfort. Large meals were especially disturbing, and he voluntarily restricted his diet as much from fear of postprandial discomfort as from a lessened appetite. November 15, 1919, he discontinued work because of the pain and weakness. His dyspepsia persisted and was actually progressive in spite of a markedly restricted diet, chiefly consisting of toast, milk, and raw eggs. There were no nocturnal pains. The bowels were quite regular as usual. At irregular intervals after meals the patient had pyrosis or salivation. He lost 17 pounds in weight. During the three weeks prior to coming under our observation he lived chiefly on milk toast.

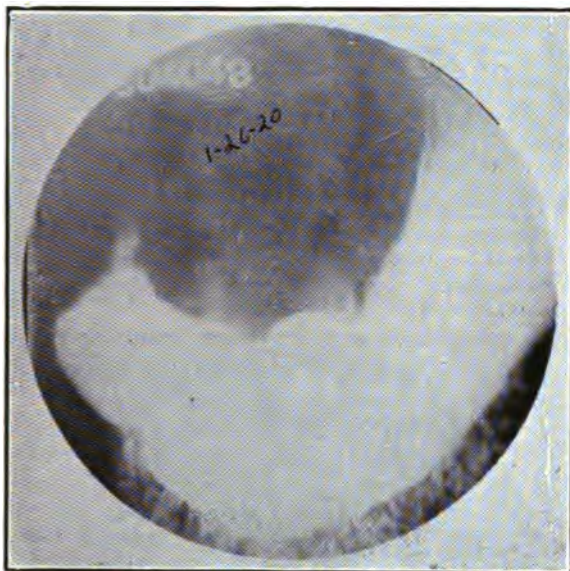


FIG. 36 (Case A304048).—Roentgenogram January 26, 1920. Gastric ulcer on the posterior wall of the body of the stomach, No. 2 retention; niche of the ulcer was not seen in the roentgenogram. A diagnosis was made on the fluoroscopic findings.

Physical examination revealed considerable dental repair, chronic tonsillitis, irregular pupils but good reactions, cervical and axillary adenitis, tenderness high in the middle line of the epigastrium, a left inguinal hernia, a few external hemorrhoids, and moderate prostatic hypertrophy. Urinalysis, blood pressure, thoracic organs, and superficial and deep reflexes, were objectively negative. The veins of the fundus of the eye were full and tortuous. Fractional gastric analysis revealed a slightly subnormal acid curve and a tendency to moderate hypersecretion. Pathologic elements were not found on chemical or microscopic examination. A Wassermann test on the blood serum showed total inhibition of hemolysis. Roentgenograms, January 26, 1920, demonstrated a No. 2 six-hour barium retention. The niche of the ulcer which was on the posterior wall of the stomach was not seen, but was diagnosed on fluoroscopic findings.

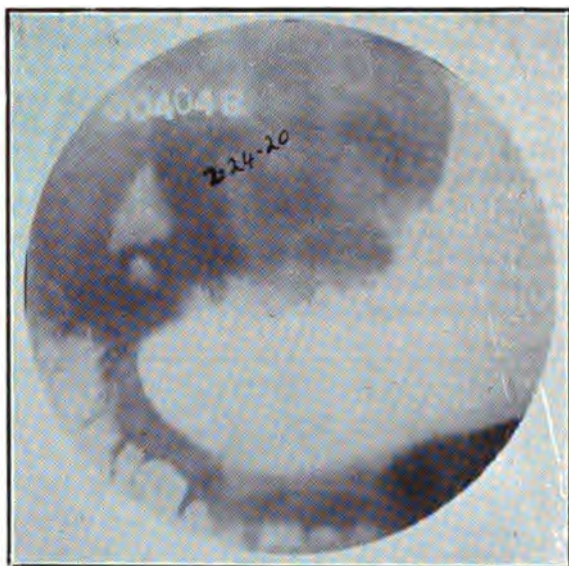


FIG 37 (Case A304048).—Roentgenogram February 24, 1920. Findings the same as in the roentgenogram in Figure 36 except that the retention was No. 1.

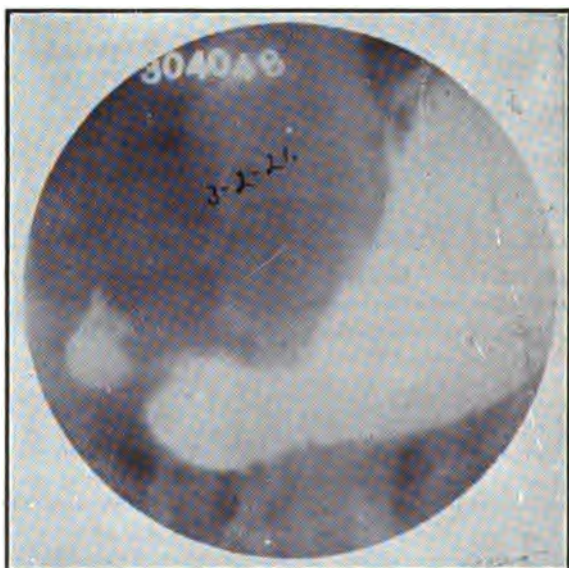


FIG. 38 (Case A304048) —The roentgen examination March 2, 1921 was negative. Both at the second and third examinations it was noticed that the stomach had diminished in size.

Following medical and surgical consultation in which the possibility of a benign, malignant, or syphilitic ulcer was under serious consideration it was decided to institute intensive treatment for syphilis; in the event of unsatisfactory response surgical interference would be reconsidered. Between January 31, 1920 and March 6, 1920, the patient received six intravenous treatments of arsphenamin under the direction of Dr. Stokes and his associates. The patient later stated that on the sixth day after the first injection all his gastric symptoms disappeared, and that he had gained 28 pounds, an average of one pound each day. February 24, 1920, a second roentgen examination showed that the niche had become considerably smaller, and the six-hour retention was less. March 1, 1921, the patient returned at our request for another examination. In the meantime he had had forty mercurial inunctions self-administered. His health had been excellent since his first visit; his weight was 141 pounds. Gastric analysis revealed normal acid values and good motility. Reray of the stomach March 2 and March 5, 1921, by Dr. Carman, revealed normal conditions, but the Wassermann reaction again was strongly positive. A second course of six intravenous arsphenamin treatments was given between March 7 and April 11, 1921 (Figs. 36, 37, and 38).

DISCUSSION

Gummatous tumor and round ulcer until recently have been the popular pathologic conceptions of gastric syphilis. Before the era of serology and roentgenology the clinical diagnosis of syphilitic round ulcer of the stomach was frequently made and such well known observers as Ewald, Fenwick, and Neumann were authority for the statement that from 5 to 20 per cent of their cases of chronic ulcer were syphilitic. Other writers, however, would not ascribe to such a high percentage, and, on the basis of pathologic studies by Chiari, Fraenkel, and others since then, the earlier percentages are unquestionably too high. That gumma or gummatous tumor, which was practically the only anatomic lesion of syphilis recognizable by the early pathologic anatomists, is the usual type of lesion of later or latent syphilis is apparently disproved by Warthin's exhaustive investigations. He is firmly of the opinion that the viscera are involved in all cases of latent syphilis, not by gummatous processes, but by specific inflammatory processes, eventually fibrosis, usually mild in character, but acquiring pathologic importance because of this progressive character. To the clinician a proper conception of the pathologic process is of immediate diagnostic and practical importance. The coincidence of chronic ulcer of the stomach and duodenum, of gastric cancer, and systemic syphilis is not uncommon. It has been my unflinching experience that the gastric or duodenal ulcers which exhibit chronicity and hyperacidity, and with symptoms controllable by diet and alkalis, that the associated systemic syphilis, latent or active, has no etiologic relationship. This

experience is further fortified by the fact that urgent treatment for syphilis has no influence on the symptoms or structure of the ulcer and that histologic examinations of the lesions removed at operation are characteristic of benign callous ulcer. The symptomatology and rapid clinical course of the case herein reported was not unlike that of many other proved cases of gastric syphilis; it differed only in that the pathologic process was circumscribed.

Our clinical experience, combined with the evidence obtained at the operating table and in the fluoroscopic room, supports the modern conception of pathologic processes in the viscera of patients with old or latent syphilis. A circumscribed gummatous tumor (syphiloma, syphilitic gumma, and so forth) which is palpable and which, if at the orifices, may even produce obstruction, is rare in our experience. The roentgenologist has shown that this type of lesion is either rare or gives little or no distress because the majority of cases in which roentgen-ray examination is made are not of this type. For, "in lues notwithstanding the extensive distortion of the stomach, no corresponding mass can be felt, and the filling defects are evidently due not to the intrusion of a tumor, but to an infiltration and contraction of the gastric walls."² Warthin noted that the fibrosis in the tissues was very marked and associated with it were infiltration, ulceration, and cicatrization in varying degrees. Syphilitic round ulcer is probably the result either of a peripheral endarteritis or of the ulceration of a single gummatous lesion in the submucosa. These must be clearly distinguished from the more frequent, shallow, dirty, multiple ulcerations of the gastric mucous membrane over an inflammatory syphilitic process in the submucosa. Wile, in a fairly complete article dealing largely with a review of the literature on gastric syphilis, mentions a recent case of syphilitic gastric ulcer in Cabot's service at the University Hospital, Ann Arbor. The patient gave a negative Wassermann reaction, but Warthin was able to demonstrate spirochetes in the excised material.

This is our first convincing case among several thousand cases of benign ulcer of a circumscribed single deep syphilitic ulceration of the stomach. Undoubtedly the true nature of other gastric ulcers has been overlooked, but we are convinced that this type is fairly rare.

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SURGICAL MANAGEMENT OF GASTRIC ULCERS*

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The surgical treatment of gastric ulcer is characterized by a striking uniformity of results. Averages based on statistics from scattered sources show that satisfactory results are being obtained in from 70 to 80 per cent of cases of chronic gastric ulcers in which operation is performed. This average is considerably higher if we include patients whose distress has been alleviated only, so that the number failing to secure any benefit by surgical management does not exceed 5 to 10 per cent. It is this small percentage of absolute and relative failures, however, that the internist emphasizes, and that the surgeon regards as a stimulus to increasing the efficiency of surgical methods.

Certain lines of investigation and action could be followed profitably in the endeavor to make the surgical treatment of gastric ulcer even more effective. The part of focal infection in the etiology of the disease is of predominant importance, but a systematic, thorough search for an infectious focus has rarely been included in the surgical management. It is true also that the excellent results which follow operation for chronic gastric ulcer have been accomplished with little attention to postoperative dietary or therapeutic management, although it would be logical routinely to carry out an intelligent régime of diet and habits of living. Since these two unquestionably important phases in the treatment of gastric ulcer have been neglected almost entirely in the past, it seems safe to predict that with their full development the number of failures to secure a complete permanent cure will be still further diminished.

The point I wish to discuss in this paper, however, and one which I believe is of great immediate importance, concerns the selection of operation in cases of gastric ulcer. It is very probable that further progress toward maximum good results in this disease will come from the most intelligent selection and application of the methods of treat-

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ment which are now known, rather than from additional operative methods. It has become a platitude that the surgeon should have no fixed ideas of the operation he will perform in gastric ulcer until the lesion is revealed. The recent plea by British and European surgeons, notably Moynihan, for more frequent employment of partial gastrectomy for gastric ulcer indicates how unsettled is the question of the most efficient use of the various surgical methods of dealing with the lesion.

The observations in this paper are based on the results of the surgical treatment in 826 cases of gastric ulcer in the Mayo Clinic between January, 1913 and January, 1920, and they are intended to point out, as specifically as possible, the relative merits of surgical measures of proved value and some of the indications for their selection.

There are four main considerations on which the value of any operation for gastric ulcer should be judged: simplicity, applicability, immediate results, and ultimate results.

SIMPLICITY

The simplicity of an operation depends on the ease with which it is performed and the soundness of the principles on which it is based. The popularity of gastro-enterostomy is due largely to the fact that it excels in these two respects. Under ordinary circumstances the operation is simple and safe, and its chief purpose, affording rest to the stomach, is fundamentally sound. The value of the relative rest which is brought about by gastro-enterostomy has not been sufficiently recognized, and yet it is probably the most important function of the operation. Absolute rest of the stomach can be secured by a jejunostomy, and Moynihan advocates and employs this procedure combined with gastro-enterostomy in "Y" for very large fixed ulcers in patients in such poor condition that all other procedures are contraindicated; he reports excellent results of such management. The relative rest afforded by gastro-enterostomy alone, however, seems to be quite sufficient, in all but exceptional cases, to create conditions favorable to the healing of the ulcer.

Another operation which stands out prominently because of its ease of performance is cautery excision; it also is based on sound premises, namely, the effect of heat on infected and malignant tissue. Inasmuch as it is now generally recognized that the best treatment for chronic gastric ulcer must include its radical removal, combined with

some procedure to insure symptomatic relief and to prevent recurrence of the ulcer, it is fortunate that we have at hand such simple, safe, and effective measures as cautery excision and gastro-enterostomy, the combination of which has been attended by such satisfactory results. Compared with these procedures, partial gastrectomy, particularly when combined with gastrojejunostomy in "Y," is primarily at a serious disadvantage for the chances of mishap during its performance are too many to warrant adoption of the operation by any but the most skilled and experienced surgeons.

APPLICABILITY

No operation compares with gastro-enterostomy in its applicability, for often it can be employed when all other procedures are contraindicated, as in an extensively indurated, adherent ulcer high on the lesser curvature, for which resection is not feasible, excision unwarranted, or even destruction by cautery not easily carried out. Not only can gastro-enterostomy be performed in such cases, but the results may be expected to be satisfactory in a large proportion of cases. The wide applicability of the operation and the likelihood of its bringing about good results has naturally led to its being performed when conditions definitely contraindicated it, and especially when no ulcer existed. The extent of its abuse may be surmised from the fact that it has been found necessary to cut off a number of gastro-enterostomies in the Mayo Clinic because the operations had been performed unwisely. When the operation is indicated there are fewer obstacles to its performance than to any other procedure. Even when the stomach is small and high-lying, and cannot be easily approximated to the jejunum, the anastomosis can be accomplished without undue difficulty. During the last seven years gastro-enterostomy has been a part of the surgical management in 82 per cent of the operations for gastric ulcer in the Mayo Clinic, excluding gastric resections.

IMMEDIATE RESULTS

One of the most remarkable accomplishments in the surgical management of benign lesions of the stomach has been the steady reduction of operative mortality. The elimination of former dangers directly associated with the operation, namely, hemorrhage, sepsis, and mechanical disturbances, has been largely responsible for the present low average mortality for all types of operation in all gastric ulcers, acute, perforat-

ing, and chronic, 2.99 per cent. This percentage has varied but little during the past five years, so that even with more effective pre-operative and postoperative treatment and more careful selection of operation such improved methods affect the general mortality rate by only a small margin. The low mortality rate of 1.85 per cent in 213 cases of cautery excision and gastro-enterostomy in the Mayo Clinic during a period in which the indications for this operation were not so well known as they now are, is significant. On the other hand, partial gastrectomy for ulcer has been associated with a considerably higher mortality than that following knife or cautery excision and gastro-enterostomy; but it should be stated that it has been the practice in the Clinic to resect the stomach only in cases of ulcer with serious complications or those suspected of malignancy. All operative procedures for gastric ulcer are so perfected now that the immediate convalescence of patients is rarely disturbed and serious complications, such as hemorrhage, vomiting, and mechanical difficulties at the anastomosis, have been practically eliminated.

ULTIMATE RESULTS

It is chiefly in relation to ultimate results that the plea for more radical surgical methods than gastro-enterostomy is made, and the question is mainly whether or not the disadvantages of gastric resection, particularly its greater difficulty and its higher immediate mortality, are outweighed by any superior ultimate results which may follow the operation. Ultimate results may be considered under three headings: (1) relief of symptoms; (2) protection against recurrence of the ulcer or occurrence of a new ulcer; and (3) protection against the development of cancer.

Relief of symptoms.—It is fortunate that the results of operation for gastric ulcer, so far as the relief of symptoms of which the patient complained is concerned, can be ascertained readily and accurately without reëxamination of the patient. Certain points in connection with such results may be emphasized: (1) Experience has shown that if a patient has had complete relief for a year after operation, it is very unlikely that symptoms will recur, so that statistics and observations based on results after at least eighteen months are relatively accurate. (2) A point to which I have drawn attention in a previous paper² is that some patients, although completely relieved of their symptoms, may suffer from gastric hemorrhages at a later period, this tendency being greatest

in patients who have reported hemorrhages previous to operation. It is imperative, therefore, to deal radically with the bleeding type of ulcer, and since we have made a routine practice of destroying every ulcer, duodenal as well as gastric, associated with a history of bleeding, the incidence of these unexpected hemorrhages has been greatly reduced. (3) Of the patients who did not obtain a completely satisfactory result from the operation very few have not been accorded a greater and more lasting measure of relief than they had secured from any previous medical treatment. It is not difficult, if one seeks to find evidence that will appear unfavorable, to obtain statements from patients that they occasionally have some gastric disturbance following operation, which on fair consideration has no more significance than have similar disorders in persons in normal health. Such disturbances are cited, however, as evidences of surgical failures by those who endeavor to discredit surgery or to discredit a certain type of operation. The final judgment of what the operation has accomplished for the relief of symptoms can safely be based on the opinion of the patient.

Protection against recurrence of ulcer, or against occurrence of a new ulcer.—Gastrojejunal ulcer after gastro-enterostomy, for example, has been so emphasized, because of the numerous papers on the complication, that a quite unjustified reaction toward this operation has resulted. It is apparently forgotten that ulcers occasionally recur and new ulcers occasionally form after any type of operation for gastric ulcer. Some known factors which contribute to the formation of ulcers in the line of anastomosis are the irritation of permanent suture material, unnecessary trauma caused by clamps or forceps, and a neglected hematoma. These are controllable factors, but the greatest advance toward preventing the occurrence of these new ulcers will be, I believe, the routine eradication of all septic foci and the adoption of a proper postoperative dietary and therapeutic régime. The complete protection against recurrence of ulcers in any part of the stomach probably depends largely on the thoroughness of such measures.

Protection against cancerous degeneration.—The danger of cancer developing on a gastric ulcer for which gastro-enterostomy alone has been performed has been variously estimated. Kocher placed the figure at 2 per cent, von Eiselsberg at 4 per cent, while Coffey has found recently that in his own large experience cancer actually developed more frequently in cases in which excision was performed than in cases in which gastro-enterostomy alone was performed; the latter

incidence was only one in 163 cases. Our records show that in 214 cases of simple gastro-enterostomy for chronic gastric ulcers there were five patients in whom death from cancer occurred more than two years after operation. It must be remembered, however, that the percentage of late deaths following gastro-enterostomy is higher than the percentage following any other operation. While it is not known how many in the former group die of gastric cancer, it is fair to assume, because of the absence of proof of the true character of the lesion at the time of operation, that a considerably larger number die of cancer than is known. One of the most interesting questions in this connection is whether gastro-enterostomy alone, for an ulcer which has already taken on early malignant changes, does not, besides healing the ulcer, delay growth of the cancer cells already implanted. There is some evidence to show that this occasionally takes place, but very little evidence to support the view that cancer frequently develops on a really benign ulcer which has been gastro-enterostomized. From all information we have been able to obtain on the subject, we have found that cancer has been known to develop, during a seven-year period, in thirty-three of the 799 cases of gastric ulcer in which operation has been performed in the Mayo Clinic. These known cases of cancer developed after every type of operation, and, what is of great importance, with apparently no less frequency following partial gastrectomy than following knife or cautery excision and gastro-enterostomy. This entire question of subsequent results in relation to the different operations needs continued study. There is one certain fact, namely, that no operation for gastric ulcer will absolutely assure a patient that he will not die from gastric cancer. Whether the incidence of cancer after any operation which includes radical removal of the ulcer is any higher than the normal incidence of the disease remains to be settled and, if proved, explained.

This review of the relative merits of the various methods of dealing with certain types of ulcers and the attempt to establish indications for the operations, are based on the experience with these methods in the Mayo Clinic, and a study of their immediate and late results.

ULCERS OF THE LESSER CURVATURE

Ulcers of the lesser curvature, including those closely associated with the lesser curvature on the anterior or posterior wall, comprise

almost 90 per cent of all gastric ulcers. Small ulcers of the lesser curvature, that is, ulcers with craters less than 1 cm. in diameter, when situated in the pars pylorica or pars media, and without extensive induration or perigastric adhesions, have been best managed, in our experience, from the standpoint of immediate and end-results, by knife or cautery excision combined with gastro-enterostomy. From the standpoint of operative management cautery excision has certain distinct advantages over knife excision, and the late results of cautery excision combined with gastro-enterostomy, when the procedure has been wisely chosen, are at least as good as those obtained by knife excision and gastro-enterostomy.¹ If either method of excision has been performed radically, the danger of cancer developing is negligible. The value of heat as a destructive agent to the cancer cell which may already have been developed in the tissues surrounding the actual ulcer has been well established. For small ulcers on the lesser curvature in positions less easily accessible, excision, preferably by cautery, followed by gastro-enterostomy, is very satisfactory and as a matter of fact is the only radical treatment that can be carried out safely. Gastric resection is certainly not warranted in these small, high-lying ulcers because of its technical difficulties, because the amount of healthy stomach removed is out of all proportion to the size of the ulcer, and because of the efficiency of cautery excision and gastro-enterostomy. It may be doubted whether any method of surgical management of these smaller ulcers, in whatever position on the lesser curvature, will prove to be more successful than excision by cautery and gastro-enterostomy, which give satisfactory results in more than 80 per cent of the cases, and an operative mortality of only 1.8 per cent.

Ulcers of the lesser curvature with a crater larger than 2 cm. in diameter, with extensive induration, adhesions to neighboring structures and organs, and indications of possible malignancy, must be dealt with quite differently from the small, uncomplicated ulcers, in order to insure the best possible results. If a large ulcer is near the pyloric end of the stomach, pyloric resection is the operation of choice unless the lesion is so fixed to surrounding tissues and is in such an acute inflammatory state, that its mobilization is unwise. Under the latter circumstances gastro-enterostomy is clearly indicated and it will give excellent immediate results with a fair prospect of permanency. The indications for subtotal gastrectomy become less clear the farther an ulcer of this type is from the pylorus, although as long as such an ulcer

is reasonably accessible and can be mobilized safely, gastric resection is the best procedure. Beyond this point of reasonable accessibility, resection is inadvisable because of the reasons already mentioned, and because of the distinctly additional risk. When the lesion is in the body of the stomach and is associated with hour-glass deformity, resection in continuity is a useful technical procedure which will give good immediate results, but sometimes the ultimate results in our experience have been marred by disturbances in motility due to contracture in the site of anastomosis. Deaver and Pfeiffer have recently reported better results from this operation by adding a gastro-enterostomy distal to the circular anastomosis.

The selection of the best operation for the small, uncomplicated ulcers and the large, complicated ulcers of the lesser curvature is not difficult. When an ulcer between these two types is met with on the lesser curvature, however, the best operation is not so easily chosen. Again the important question is that of malignancy. There are no hard-and-fast rules by which early malignant changes in an ulcer can be recognized, so that differentiation is not easy or certain, but it is a fact that the subsequent course of doubtful cases shows that errors in interpretation are rarely made, and when they are it is much more likely that an ulcer has been erroneously labeled "cancer" than a cancer mistakenly called "ulcer." The danger of a primary gastric cancer or a cancerous ulcer being wrongly diagnosed or unrecognized by the combined findings of a well-qualified internist, a roentgenologist, and a surgeon, I believe to be most unlikely, and it is surprising how few of the gastric lesions diagnosed clinically, roentgenographically, and at operation as benign ulcers, prove to be malignant on pathologic examination following radical removal of the ulcer. The incidence of such cases in the Mayo Clinic has not exceeded 1 or 2 per cent. The method of removing a substantial slice from the ulcer and subjecting it to immediate microscopic examination, while not absolute in determining whether malignancy is present, has proved to be most valuable and is quite justified, providing the ulcer is immediately destroyed by cautery, whether or not malignancy is reported on pathologic examination. This procedure is carried out routinely in the Clinic in cases which really are not suspicious of malignancy, adding, of course, a gastro-enterostomy. If, however, any part of the examination raises the possibility of malignancy, if the ulcer is favorably situated for resection, and conditions warrant it, partial gastrectomy holds first

place, although the higher operative risk demands that the operation be well justified before it is attempted. The farther from the pylorus ulcers in this borderline group are encountered, the less definite become the indications for subtotal gastrectomy, particularly for the surgeon whose experience has not been large in this field. The best surgical management of these cases is, I believe, gastric resection when proof of malignancy is established; gastric resection, if it can be performed without an abnormally high mortality, when there is strong suspicion of malignant degeneration; radical cautery excision and gastro-enterostomy, if the resection cannot be performed without an abnormally high mortality; and, in all other cases, cautery excision and gastro-enterostomy, except in cases of ulcer so near the cardia that access is too difficult, when gastro-enterostomy alone will often give surprisingly good results. In cases of very extensive ulcer the usefulness of jejunostomy should be remembered.

ULCERS OF THE POSTERIOR WALL

After the lesser curvature the most common site of ulcer is the posterior wall: about 10 per cent of all gastric ulcers occur there, and 75 per cent of these are in the pars media. The surgical management of these is technically more difficult and is not as yet attended by as satisfactory results as follow operations for ulcers of the lesser curvature. Such ulcers usually have extensive craters and are attached to the pancreas, and the patients are often in poor condition. It is a requisite of any operative procedure undertaken for such ulcers that the stomach and pancreas shall be separated if good results are to be obtained. This separation may be accomplished by various approaches such as transgastric, through the gastrohepatic omentum, or through the transverse mesocolon. W. J. Mayo has recently stated his preference for the gastrohepatic omentum approach because it is simplest, most applicable, and most effective in exposing the ulcer and its attachments. The ulcer having been separated and specimens removed for microscopic examination, the edges of the opening in the stomach should be removed thoroughly by cautery, the raw surfaces of the pancreas seared, the opening in the stomach closed, and gastro-enterostomy performed. If cicatrization has developed to a point in which there is hour-glass deformity in the body of the stomach and the ulcer itself cannot be dealt with satisfactorily, sleeve resection combined

with gastro-enterostomy deals very adequately with the pathologic condition and with the deformity, although symptomatic relief is not certain. When ulcers of the posterior wall are situated near the pylorus (only 8 per cent of them are in this situation) pyloric resection is the operation of choice.

ULCERS OF THE ANTERIOR WALL

Ulcers of the anterior wall constitute only 1 per cent of gastric ulcers. If the ulcer is small it can be excised primarily with the knife or cautery and direct closure made, or, if the ulcer is near the pylorus, a plastic operation may be advisable. The pyloroplasty of Finney has a definite application in small, nonadherent ulcers in close proximity to the pylorus, although its value seems to be chiefly in dealing with ulcers of the duodenal side of the pylorus rather than on the gastric side. The operation permits of radical removal of the ulcer and direct inspection of the posterior wall of the stomach and duodenum.

For large ulcers of the anterior wall near the pylorus, especially when they have perforated and become adherent to organs and structures, pylorotomy is justified if the mobilization does not involve too wide a dissection into inflammatory tissue; but it should be remembered that these "pyloric" ulcers are almost always duodenal and hence not subject to malignant changes. The same indications for pylorotomy exist when malignancy is suspected or proved, as I have already pointed out. If pylorotomy is not advisable gastro-enterostomy alone, without separation of the ulcer from its attachments or any radical treatment of it, is the operation preferred. Should a diagnosis of malignancy or probable malignancy be made at operation and it seems unwise, because of the patient's condition or the condition of the operative field, to resect the growth, gastro-enterostomy may be performed as a first-stage operation in anticipation of performing resection as the second stage when conditions are favorable. Nothing illustrates so well what gastro-enterostomy will accomplish as its visible effect on these large, adherent lesions; and experienced surgeons all testify to the fact that when the abdomen is opened for the second stage, these ulcers, supposedly malignant, have occasionally entirely disappeared.

To the few remaining types of ulcers of the anterior wall and of the greater curvature the general principles that have been suggested may be applied.

The indications outlined for the choice of operation in gastric ulcers of various types and situations are necessarily somewhat general; but they are based on a careful study of the results of operations for 826 gastric ulcers in the Mayo Clinic during a seven-year period. It seems quite safe to conclude from these results that there is every justification for adhering to the practice of excising, preferably by cautery, the benign chronic gastric ulcer, and combining a gastro-enterostomy with the excision. The results in this series of cases do not indicate that more radical treatment, gastric resection, is a preferable method in any considerable percentage of nonmalignant ulcers.

It is encouraging to note in summarizing that we were able to trace 85 per cent of the patients in this series. More than 70 per cent report complete relief, 10 per cent report improvement, and 4 per cent only report no relief.

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THE PREVALENCE OF FREE HYDROCHLORIC ACID IN CASES OF CARCINOMA OF THE STOMACH*

HOWARD R. HARTMAN

Achlorhydria is so frequently associated with carcinoma of the stomach that one acquires the habit of looking for it as a diagnostic sign of carcinoma. This habit grows until one hesitates to make a diagnosis of carcinoma of the stomach in the presence of any appreciable amount of free hydrochloric acid in the gastric secretions. Clinicians who have the opportunity to observe the results of fractional analysis of the gastric contents find that achlorhydria is not essential to the diagnosis of gastric carcinoma. As a means of corroborating this finding a statistical review was undertaken of the analysis of gastric contents in cases in which operation was performed for cancer at the Mayo Clinic during the years 1918, 1919, and 1920. Since the results for each year were quite uniform the data were studied as a whole. When the surgeon noted the location of the lesion in the pyloric, middle, or cardiac portion of the stomach this was considered in classifying the data.

During the three years there were 551 patients with gastric carcinoma and eighty patients with carcinomatous ulcer operated on. Of the latter, with one exception, a case diagnosed gallstone, a gastric lesion was clinically suspected. Forty-five per cent of the cases were diagnosed ulcer, 41.25 per cent cancer, and in 12.15 per cent the diagnosis was suspected gastric malignancy.

The gastric secretions were first classified separately according to the type of the lesion and then together. Of the 551 patients with carcinoma forty-seven did not have test meals because they were too weak to stand it, because the stomach was found empty on aspiration, because of a mistaken diagnosis, because the patient's condition demanded an emergency operation, and so forth. In 122 patients the lesions were not located by the surgeon, although resection was per-

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formed. In sixty-six the condition was found inoperable. An exploration or a gastro-enterostomy only was made for relief of an obstruction. In 297 patients the lesions were in the pyloric end of the stomach, in twenty-seven in the middle portion, and in thirty-nine in the cardiac end. These data were taken from patients who were operated on; this accounts for the preponderance of pyloric lesions which are favorable for surgical measures, whereas lesions higher up are not accepted by the surgeon (Table 1).

The normal amount of free hydrochloric acid was estimated at from 20 to 40. The classification of the lesions according to location revealed little of importance. However, in 51.85 per cent of the pyloric lesions achlorhydria was present, and the pyloric end of the stomach is not supposed to possess any acid-forming cells that could be destroyed by a new growth. In 5.05 per cent of the pyloric lesions the values were hyperacid. In the cardiac portion, which is supposed to possess some of the acid-forming cells, the achlorhydria was 61.54 per cent and the hyperacid values 5.12 per cent.

The location of the lesion apparently does not materially influence the degree of the acidity. It is impossible from these statistics to determine the percentage of occurrence of any one degree of acidity in any one division of the stomach. Pyloric lesions predominate in patients operated on and, therefore, they have the highest percentage occurrence in any one degree of acidity.

Attention is called to the total findings in Table 1 in which the gastric analyses have been studied without reference to the location of the lesion. Only 53.72 per cent, about one-half of the patients, had achlorhydria; 15.78 per cent had free hydrochloric acid in small amounts. In 17.42 per cent the gastric acidity was normal, that is, 20 to 40, and 4.53 had hyperacid values. The sum of the last two figures show that 21.95 per cent, or more than one patient of five, had normal or hyperacid values. Thirty-seven and seventy-eight hundredths per cent, or about two of five patients, had a certain amount of free hydrochloric acid. The occasional marked difference between free and total acidity is shown in Table 2; this occurs particularly in pyloric lesions. It cannot be explained by obstruction with retention of the neutralizing foods, because in the cases in which the difference in the acidity was more than 40 there was obstruction only in 34.28 per cent.

In Table 3 are data concerning gastric ulcer undergoing malignant change. Only 22.50 per cent of patients had hypo-acid values. The

sum of the percentages of those having some acid (hypo-acidity, normal acidity, and hyperacidity) is 72.50. The extent of the malignancy, therefore, seems to influence the amount of free acid because the corresponding total in patients with carcinoma was only 37.78 per cent.

In Table 4 it may be seen that of 631 cases of gastric carcinoma in all stages of development 49.76 per cent showed achlorhydria, 15.21 per cent hypo-acidity, 19.96 per cent normal acidity, and 6.97 per cent hyperacidity. The sum of the last two figures shows that 26.93 per cent or about one case out of four had normal or hyperacid values. Forty-two and fourteen hundredths per cent had some free hydrochloric acid present. One should expect then to find free hydrochloric acid in about every other case.

It is seen, therefore, that achlorhydria is present in a little less than one-half of the cases of carcinoma of the stomach. Normal or hyperacid values can be expected in more than one-fourth. The acid values represent the highest reading obtained by a fractional analysis of the gastric contents; this I believe gives a greater chance of obtaining higher, more accurate values than the single tubing.

TABLE 1
CARCINOMA

	Cases.	Per cent.	Achlorhydria.	Per cent.	Hypo-acidity.	Per cent.	Normal.	Per cent.	Hyperacidity.	Per cent.	No test meal.	Per cent.
Not located.....	122	22.14	67	54.9	12	9.83	22	18.+	4	3.27	17	13.9
Inoperable.....	66	11.97	40	60.6	8	12.12	11	16.66	4	6.06	3	4.54
Pyloric.....	297	53.9	154	51.85	53	17.84	54	18.18	15	5.05	21	7.07
Middle.....	27	4.9	11	40.74	11	40.74	5	18.51				
Cardia.....	39	7.07	24	61.54	3	7.69	4	10.25	2	5.12	6	15.38
Ignoring location...	551		296	53.72	87	15.78	96	17.42	25	4.53	47	8.53

TABLE 3
CARCINOMATOUS ULCERS

	Cases.	Per cent.	Achlorhydria.	Per cent.	Hypo-acidity.	Per cent.	Normal.	Per cent.	Hypersacidity.	Per cent.	No test meal.	Per cent.
Not located.....	22	27.50	6	27.27	3	13.63	5	22.72	7	31.36	1	4.54
Inoperable.....												
Pyloric.....	50	62.5	10	20.0	6	12.0	22	44.0	12	24.0		
Middle.....	3	3.75	1	33.33			2	66.66				
Cardia.....	5	6.25	1	20.0			1	20.00			3	60.00
Ignoring location...	80		18	22.50	9	11.25	30	37.5	19	23.75	4	5.0

TABLE 4
CARCINOMA AND CARCINOMATOUS ULCERS

	Cases.	Per cent.	Achlorhydria.	Per cent.	Hypo-acidity.	Per cent.	Normal.	Per cent.	Hypersacidity.	Per cent.	No test meal.	Per cent.
Not located.....	144	22.82	73	50.69	15	10.41	27	18.75	11	7.63	18	12.5
Inoperable.....	66	10.45	40	60.6	8	12.12	11	16.66	4	6.06	3	4.54
Pyloric.....	347	54.99	164	47.26	59	17.0	76	21.9	27	7.78	21	6.05
Middle.....	30	4.75	12	40.0	11	36.66	7	23.33				
Cardia.....	44	6.97	25	56.81	3	6.81	5	11.36	2	4.5	9	20.45
Ignoring location...	631		314	49.76	96	15.21	126	19.96	44	6.97	51	8.08

CARCINOMA DEVELOPING ON GASTRIC ULCER*

CHARLES H. MAYO

Cancer continues to take its deadly toll from human life. In this country more than 80,000 die yearly from the disease; nearly a million lives have been thus sacrificed in the last decade. Cancer is the dread disease of middle life and of old age, made so by the prolonged suffering which accompanies it. The dread is far worse than the brief period of fear in times of pestilence, or of fear of sudden death from cardiac disease. Whether the increase in the disease is real from some defect in advancing civilization, or whether it is more apparent because of increased knowledge from closer observation, and more accurate statistical reports is a question. The work of the Committee on Cancer Research of the American Medical Association and various commissions composed of interested investigators has done much to educate the public concerning the condition, its treatment, and especially its prevention. Members of the medical profession are paying greater attention to the relief of recurring chronic local inflammation and to the removal of sources of local irritation, believed to be concerned in the development of cancer. Through these influences a greater number of patients appear for operation earlier, at a time when the disease is preventable or curable. Cancers, from the standpoint of heredity, while they are interesting in lower life, are fewer than the general law of averages in man.

HISTORICAL

A review of the literature concerning cancer is exceedingly interesting from a historical standpoint and calls to mind that old saying, "There is nothing new under the sun." The earliest records concerned only the treatment of the disease. In Egypt, India, and Persia the condition was recognized 1500 B. C., when the Egyptians applied arsenic paste in its treatment, a remedy used internally and externally many

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centuries later. Hippocrates excised cancer with the cautery as early as 400 B. C., a method still in use as a general destroyer of carcinomatous tissues. Celsus at the time of the birth of Christ employed the knife for the clean dissection of cancer, and vessels were ligated to check the growth of inoperable tumors, a method revived a few years ago by the late Dr. Dawbarn of New York. In the second century, Leonides used the knife and cautery in clean dissections. From that time little was added to the treatment of cancer until the recent development of serum therapy, endocrine therapy, roentgen treatment, and radium emanations. From what has been accomplished in the brief period of their use, especially by radium, I predict the possibility of surgery becoming an adjunct to these methods instead of the major method of treatment.

ETIOLOGY

From the point of view of etiology, Galen, in the second century, considered that the body consisted of solids and four fluids, blood, mucus, yellow bile, and black bile. He believed that the concentration of the latter was the cause of cancer, a theory which held sway for many centuries, when it was refuted by Paracelsus, who substituted that of a local concentration of mineral salts as an exciting cause of the disease. If we substitute cholesterol for mineral salts we have a modern point of view for special stimulus of cell growth. The seventeenth century witnessed the development of the lymph theory of cancer, in which the lymph-node involvement was given some prominence. The acid theory, namely, acid as a stimulus to cell growth, which is under discussion at the present time, was advanced in Germany at an early period by Helmont and by Ettmüller.

In a consideration of this theory, it should be appreciated that in the normal acid areas of the body occur the greatest number of cancers; thus, in the organ of highest acidity, the stomach, are probably one-third of the cancers of men, and more than one-fifth of the cancers of women. In the large bowel are many cancers as compared with the few in the alkaline small bowel. In the urinary bladder tumors are common, as they are in the uterine cervix, which is bathed by fluids of increased acidity during the ten years preceding and following the climacteric. Within the tissues subject to normal degeneration, such as the uterus and the mammary gland, the acids formed by lipid degeneration, a well-known chemical process, may be a possible local factor

to stimulate cell growth. In this connection the work of Loeb in pathogenesis is of interest. He immersed the unfertilized eggs of sea urchins in sea water acidulated to 1 per cent with various acids, of which butyric acid was the most active, and then returned the eggs to sea water for development, and a goodly percentage of the eggs became fertilized and developed.

The general use of the microscope, from its development in 1592, made possible a minute study of the disease, and education advanced rapidly as the printing press recorded hypotheses and facts. The influence of coal smoke impregnated with sulphur has been extensively investigated in several districts of England and also in our own country



FIG. 39.—Carcinoma, 3 mm. in diameter, on the border of a gastric ulcer, 2.5 by 2 by 0.5 cm. in diameter.

as a possible external factor increasing the development of cancer. In 1775, Pott described the first occupational cause of cancer, the work of the chimney sweep. Several instances of such development have been noted since then. The influence of fluids bathing cells in cancer environment was recorded by Maunvir in 1820; he asserted that the cells arise from morbid fluids which bathe them. While this is now refuted for cancer, it is believed by some, including myself, that a change, not necessarily morbid, in the fluid bathing the embryo, is a possible cause of congenital or embryologic malformation. Malformations of the nervous system in fresh-water frogs were studied by Loeb by developing their fertilized eggs in 0.6 and 0.7 per cent solutions of salt water.

PROGRESS IN INVESTIGATION

The importance of recurring local inflammation as a field for cancer development was appreciated by Broussais. Recamier investigated infiltration, and used the word metastasis in describing growths arising from parent tumors. Virchow developed an accepted foundation for the study of cancers and other tumors. He stated, in 1860, that all cells come from preceding cells, but he made the mistake of believing that connective tissue changes into epithelium a theory which was opposed by Ramek. The cell changes from the normal through stages of involution with impairment of nutrition and loss of functional capacity, as seen in cancer, were described by Thiersch. Waldeyer advocated the theory of connective tissue isolation of a few epithelial cells, either internal or external, as the origin of cancer, which harmonizes with Thiersch's theory of nutritional changes, and was also strongly supported by Ribbert, and showed that it harmonizes with the origin of cancer of the stomach in isolated cells separated in the snare of connective tissue in a chronically inflamed field. He also demonstrated the foundation of secondary tumors as a continuous growth through blood and lymph vessels as well as transmission by cell emboli. Clinical observations concerning such distribution of cancer of the stomach show that approximately 20 per cent, or more, of such cancers are confined to the stomach until death occurs from obstruction, perforation, and peritonitis. In such cases there is no clinical evidence of metastasis in the lymph glands, liver, and distant or adjacent viscera. They compose a group favorable for operation with increased prospect of permanence of cure, except as the operation is modified by the extent of the involvement or the high location of the disease.

Ewing, in discussing glandular involvement in gastric cancer, quotes Verse as finding accidentally, at necropsy, twelve cases of early cancer of the stomach without glandular involvement, and Cuneo, as finding lymphatic invasion at necropsy in eight cases of gastric cancer, but in thirteen gastrectomies only two. The theory of tumor development from misplaced embryonal cells, known as Cohnheim's theory, became obsolete following Waldeyer's work, although the statement of Durante, made in 1874, that all tumors arise from embryonic cells or immature cells and that tumor cells have some relation to sex cells is generally acceptable. In plant life nothing more is required to stimulate local

areas into normal tissue growth than extensive cell destruction; the injury or loss of epithelium itself is apparently one of the greatest stimulations to activity of reproduction of marginal cells, for example, development of callus and normal repair of injury. The theories of bacterial and parasitic causes of cancer development as originally advocated have not been proved. I believe that the chemical action of bacteria and not their mere presence should be considered as an irritative agent of connective tissue formation and a possible source of chemical stimulation, such as toxin or other product of their activity. The specific bacterial agent of several diseases has been discovered within but a few years after many years of search.



FIG. 40.—Low power photomicrograph of (a) carcinoma on the border of the ulcer, associated with (b) marked lymphocytic infiltration and fibrosis.

It has been noted that the previously traumatized epithelial areas are much more susceptible than normal epithelial areas to the development of cancer: for example, cancer of the uterine cervix, following laceration; cancer of the lip in areas of chronic irritation from a fissure or herpes; cancer of the tongue or cheek from a broken tooth as an irritant; the degeneration of scar tissue; cancer of the gallbladder, which is associated with gallstones in more than 85 per cent of cases, and ulcer of the stomach, in the larger number of which with a diameter of 2 cm. or more, according to MacCarty and Broders, the margins are involved by cancer. W. J. Mayo, in 1915, called attention to the hot foods and drinks taken as civilization developed, a change from the food intake of primitive people, the degree of heat often being

greater than epithelium can stand. He explains the fact that fewer women have gastric cancers, since in serving the members of their household their food becomes cooled before it is taken. There is but little difference of opinion with regard to external cancer of the breast or lip. The clinician, the surgeon, and the pathologist see them in approximately the same stages, and they see 63 per cent of cancers of the lip developing on areas of previously repeated or chronic inflammations without comment.

In discussing cancer of the stomach originating on ulcer, it is probably best to drop the percentage basis, since pathologists obtain material for examination at necropsy, of late gross lesions from which

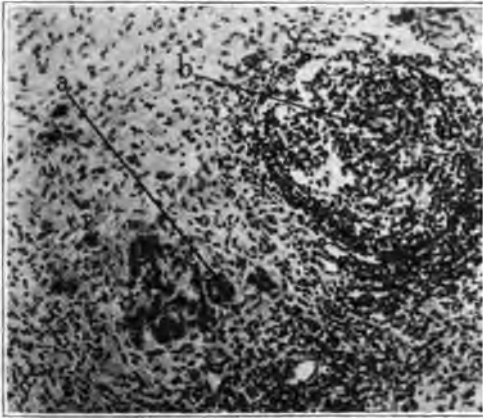


FIG. 41.—Low power photomicrograph of an area of (a) carcinoma lying near a lymph-follicle in border of ulcer.

the patient died, or of material removed surgically, and are dependent largely on the point of view of the local clinicians and surgeons with regard to the excision of the ulcer or its destruction, regardless of whether a gastro-enterostomy, or a pyloric operation is performed. The removal of ulcers by cautery (Balfour) has largely replaced excision, hence it is more difficult for pathologists to secure early specimens for examination, and instead of discussing the real problem of a possible source of cancer of the stomach, time is wasted on the discussion of the percentage of cancers of the stomach that might develop in this manner, often with their judgment based on seeing the conditions in the late stages. The modern cytobiologist has wonderfully advanced the use of the microscope in the study of the single cell, and thus with

extensive experience, is often willing to diagnose cancer on less evidence from immediate examination of frozen fresh tissue than that required by pathologists working with fixed tissue.

In the period of evolutionary life, when two or more types of cells became grouped to develop multicellular life and live a community existence, was the control over the cell a community control or an individual cell control? If it were a community control, then Cohnheim's theory of misplaced embryonal cells as a cause of the origin of cancer would be worthy of serious consideration. If it is possible that the cell is controlled by some granule within the cell, it might be exhausted or fail to appear in both parts of a cell division when exhausted by a chronic stimulus to division. I believe a biologic cause of cancer is exhausted epithelial areas induced by age, chronic traumatism, or irritation; an activating agent would be the environment, such as acid, especially butyric, one of the combined acids of the stomach and a product of lipid changes.

THE DEVELOPMENT OF CANCER

MacCarty says:

In so far as cancer (a migratory hyperplasia) is concerned, my observations have revealed a biologic reaction which is malignant only in so far as it destroys the communistic organization of cells.

The three fundamental biologic reactions to destruction (hypertrophy, hyperplasia, migration) have been found to occur not only in relation to the specific tissue of the breast, but also in relation to the specific tissues of the prostatic gland, skin, hair follicles, stomach, lymphatic glands, blood, bone, cartilage, and connective tissue. In all these chronic destruction (the biological etiological factor in cancer) of the specific tissues, calls forth hypertrophy, hyperplasia, and sometimes migration of the reserve cells.

Although these reactions may seem new in reference to human pathology, they are well known to biologists who have made a study of reaction to destruction. In fact, many biologists are of the opinion that exposure of living matter to destructive factors has led to adaptive potentialities that are the factors of safety in the structure and functions of all forms of life; nature has been just as efficient in her defensive preparation in the construction of the human body.

It may be stated as a biologic law that hypertrophy, hyperplasia, and migration are stimulated primarily by destruction. These phenomena are the effects of which destruction is the cause.

In nature the specific agent of destruction is rarely if ever anticipated. In the mammary gland and stomach destruction is the main factor, as it is with the other tissues which have been studied.

The reactionary cells of the three conditions described are apparently normal cells which answer the structural description of normal cells as found any place in nature. Their relation to the communistic organization of cells is their principal abnormal or pathologic characteristic.

It has been observed that nature provides for the regeneration of human tissues in two ways, which might be called direct and indirect, the former consisting of division of specific tissue cells, and the latter of the division of reserve cells which are set aside for the purpose of regeneration of specific tissues by the process of multiplication, specialization and differentiation. Direct regeneration of tissue represents the most primitive form of reproduction and doubtless occurs in the reproduction of endothelial tissues and perhaps some others, the reserve cells of which have not been seen. Indirect regeneration is seen in such specific tissues as those represented by squamous cells of the skin, secretory cells of the sebaceous, sweat and mammary glands, fibrous connective tissues, lymphocytes, erythrocytes, osteocytes, chondrocytes and glandular cells of the prostate, all of which specific tissues possess reserve cells which have been seen. During chronic destruction of these tissues the reserve cells react in a definite manner with a certain sequence characteristic of the behavior of living cells throughout nature. They become hypertrophic, hyperplastic, and migratory. In the light of biology these may be inter-

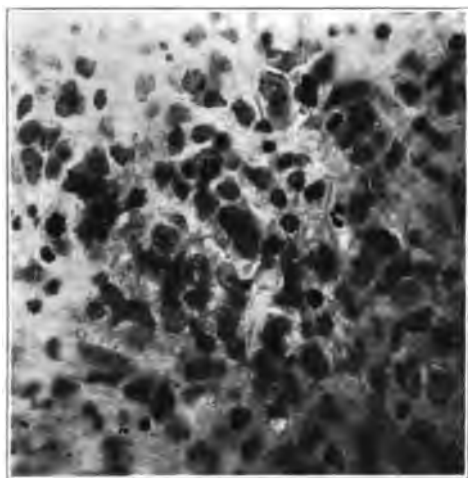


FIG. 42.—High power photomicrograph of the carcinomatous area shown in Figure 41.

preted as hyperactivity against antagonistic things or forces; increase of mass action against such antagonists, and attempt at change of environment, all of which are defensive reactions and constitute the essential means of self-preservation.

Williams states that 60 per cent of cancers of the stomach occur at the pylorus, where only 12 per cent of ulcers occur. Welch reports 36.5 per cent of ulcers just above the pylorus, where 12 per cent of cancers occur. This shows the greater influence of trauma on fewer ulcers in the more active areas of the stomach. In considering the influence of environment, practically five ulcers occur in the acid-reducing first portion of the duodenum to one in the stomach. At the Mayo Clinic during the years 1919 and 1920, 3,463 duodenal and gastric

ulcers were diagnosed. Of these, 1,673 were operated on. Fifty-eight patients had both gastric and duodenal ulcers, 1,352 had duodenal ulcer alone, and 263 had gastric ulcer alone. The percentage of mistakes in diagnosis, as shown by operation, is exceedingly small. The duodenum is resistant to cancer. The few cancers in this region occur as a rule in adenomas, or in a duct entrance, rarely in ulcer. The influence of the duodenal secretion which passes into the stomach through the gastro-enterostomy opening to some extent lowers the acid and changes the environment by overcoming retention. This possibly has some effect in checking the effects of irritation of ulcer or even the activity of cancer. Bamberger's statement, that of 1,025 patients who had gastro-enterostomies and who were observed for some time, only twenty-two developed cancer, should apply only to gastric ulcer. If more than eight hundred duodenal ulcers are withdrawn from this number, the twenty-two patients will be equivalent to approximately one in six.

In order to emphasize the greater danger from gastric than from duodenal ulcer the data from Hunter's report are summarized.

OPERATIVE RESULTS

In Hunter's investigation in behalf of the New York Life Insurance Company to determine a basis for insurance following operation for gastro-enterostomy for ulcer, the results of 2,431 consecutive gastro-enterostomies performed during several years at our Clinic were studied. All but 108 patients were traced, twenty-two of whom had had ulcers of the stomach. Five hundred and twenty-one patients with ulcer of the stomach were under observation for an average of three and six-tenths years. The mortality was 17 per cent; the first year it was four and one-third times the death rate in a like group in the general population; the rate diminished during the remainder of the period. One thousand, six hundred and fifty-one patients with duodenal ulcer were under observation for an average of three and four-tenths years; the mortality was 5 per cent, which is approximately that of the normal death rate of an equal number of persons in the general population of the same average age. Ninety-one persons with gastric and duodenal ulcers were under observation for an average period of three and eight-tenths years; the mortality was 15 per cent. It is impossible to state the exact cause of death in this group of cases, as the patients die at their homes and definite reports are rarely obtained.

There is a tendency to belittle the dangers of ulcer of the stomach. The condition occurs less frequently than duodenal ulcer, but is more serious. As a rule, ulcers of the stomach or the duodenum are not operated on early, but only after a complaint of some years' duration. A wide variation in the sensitiveness of the abdomen exists in various persons; some with little trouble complain bitterly. Often patients appear for a general examination because of loss of appetite, loss of weight and strength with increase in pallor and are found to have extensive cancer of the stomach without distress or appreciable bleeding. In 1919 and 1920, at the Mayo Clinic a diagnosis of cancer of the stomach was made in 1,529 cases. In approximately 54 per cent the condition was considered inoperable because of the extent of the disease, metastasis, complications, and so forth. In 162 an exploratory operation only was performed. In seventy-four gastro-enterostomy was performed for the relief of obstruction as a palliative operation. Two hundred and twenty-three patients were subjected to the radical operation of resection of the stomach. Better results could have been obtained for many of the patients had the condition been recognized earlier.

It will take years of observation to estimate fairly accurately the percentage of cancers which have occurred on ulcer, even if from one in twelve to one in six are thus developed. I believe the percentage is higher. Concerning cancer in general, it seems probable that we have sufficient data to show that several causes contribute to its development, and that irritation, partial destruction, and environment play the most important parts. In this type of cancer some degree of protection can be given to the greater percentage of patients if the disease is recognized early and is relieved.

The exact starting point of cancer of the stomach is unknown and probably will remain unknown, but the early cancers in this organ have been seen in the mucosa in the borders of chronic ulcers (Fig. 39).

Simple chronic gastric ulcers in which there are no signs of cancer are found. Similar ulcers in which the normal columnar cells of the gastric tubules are partially or completely replaced by spheroidal or ovoidal undifferentiated cells, the cells being intratubular, are also found, as are ulcers in which the ovoidal or spheroidal cells are also extratubular and hence in the stroma (Figs. 40, 41, and 42).

ERRORS IN THE ROENTGENOLOGIC DIAGNOSIS OF DUODENAL ULCER*

RUSSELL D. CARMAN

Less than a decade ago, at a time when the roentgenology of gastric cancer and ulcer had already gained definite recognition, investigation of the duodenum was considered impracticable. Today the diagnosis of duodenal ulcer is so thoroughly developed that the roentgenologist can discover the lesion with facility and with only a small percentage of error.

To discuss these errors may give a wrong impression, namely, that the diagnosis is attended with difficulty or that the roentgenologic findings are unreliable. Yet it is only by reviewing mistakes that we can learn whether it is possible to avoid them.

Laying aside the various minor and indirect signs of duodenal ulcer, there are but two trustworthy indications of this lesion. They are deformity of the duodenal contour, and the combination of retention and hyperperistalsis in a large but otherwise normal stomach. Hence, any mistakes should hinge chiefly on the elicitation or interpretation of these phenomena. The errors made are also of two classes: those of affirmation, when an ulcer is diagnosed but not found at operation, and those of negation, when an ulcer is not diagnosed but is found at operation.

Among the causes of affirmative error are the following:

1. Technical errors and difficulties: failure to fill the bulb completely, retraction of the abdominal wall, blending of the bulbar shadow with that of other portions of the duodenum or of adjacent concretions, and diagnosis on incomplete examinations.

2. Deformity of the bulb by causes other than ulcer: reflex spasm or other inflammatory processes in the right upper quadrant, extrinsic tumors, pressure against the spine, and lesions of the duodenum other than ulcer, namely, benign tumors, duodenitis, diverticulum, and cancer.

* Presented before the Radiological Society of North America, December, 1921, Chicago. Reprinted from the *Journal of Radiology*, 1922.

3. Pyloric and prepyloric gastric lesions.

4. Overemphasis of minor auxiliary signs or bias by the clinical history.

Causes of negative error comprise:

1. Technical faults in the examination: insufficient milliamperage, improper voltage, unsuitable tube, too great distance of patient from tube, neglect of the examiner to prepare his eyes, failure to use the diaphragm, and failure to examine both roentgenoscopically and roentgenographically.

2. Neglect to examine the duodenum in cases of cardiospasm, or ulcer or other lesion of the stomach.

3. Unfavorable position of the duodenal bulb.

4. Actual or apparent absence of bulbar deformity: minute ulcers, absence of spasm from the ulcer, small but apparently regular bulb due to obstruction of the distal portion of the bulb, and nonobstructive ulcer beyond the bulb.

AFFIRMATIVE ERRORS

Adequate filling of the duodenum is absolutely necessary for the demonstration of its actual contour. When the examination is made immediately or shortly after the opaque meal has been given, a method which is in common use, an incompletely filled duodenum may be mistaken for one deformed by ulcer. Of the factors promoting complete filling, free opening of the pylorus is perhaps most important. Free opening is retarded by coarse particles of food. Hence, for the examination fluid mixtures are best. After trying various mediums I have found an aqueous mixture to be the most satisfactory.

Sometimes the bulb is difficult to fill because it is unusually capacious, and persistent efforts may be required. Occasionally a patient, especially one who is apprehensive, retracts his abdominal wall so strongly that the initial outflow through the pylorus is scant, and the stomach cannot be satisfactorily manipulated to assist duodenal filling.

Manual pressure on the stomach, which I employ as a routine, inclining the patient to the right, examination in the right recumbent position, and blocking the lower duodenum with the hand or Holzknecht's distinctor, are all well known measures for assisting complete filling. David has employed the duodenal tube for this purpose. Notwithstanding all aids, satisfactory filling cannot always be secured.

Åkerlund describes an occasional looping downward of the duodenum

alongside the bulb and the combination as seen in certain projections may simulate bulbar deformity. He also mentions the shadows of gallstones or kidney stones merging with the shadow of the duodenum as a possible source of error. During roentgenoscopy it should be possible by palpation to separate and distinguish the bulb.

Caution against the diagnosis of ulcer after an examination that is lacking in thoroughness should be unnecessary. A positive diagnosis on bulbar distortion is warranted only by deformity which is constant, unvarying as to location, and virtually identical in appearance during

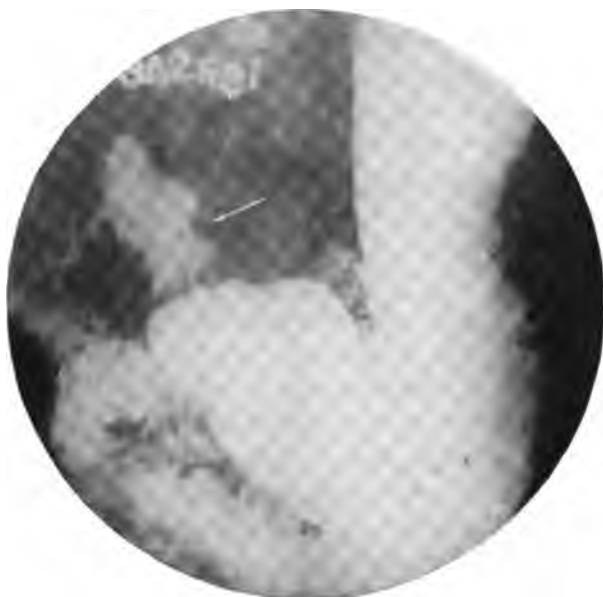


FIG. 43 (Case A342931).—Spastic deformity of the bulb, diagnosed as duodenal ulcer, in a case of chronic appendicitis.

the examination. If the examination is roentgenographic only, an ample number of plates should be made.

Spasm of the duodenum resulting from disease of other organs may produce deformity similar to that caused by ulcer. Notable among such diseases are cholecystitis and chronic appendicitis (Fig. 43). Disease of the pancreas is a possible excitant of duodenal spasm. In one of our cases of cancer of the pancreas a persistent spasm of the bulb was interpreted as ulcer. Not infrequently spasm is associated with concurrent cholecystitis and pancreatitis. Renal calculi have also been

suspected as a cause. Disease of the gallbladder or appendix is common in patients sent for roentgen examination of the digestive tract, and the symptoms often resemble those of duodenal ulcer. Fortunately duodenal spasm occurs only in a small proportion of these cases. Like gastric spasm from extrinsic causes it tends to change form and situation. In some cases that I have seen, the spastic deformity was persistent and unchanging, and caused a mistaken diagnosis of ulcer.

Pericholecystitis and other inflammatory processes in the vicinity of the bulb may distort its contour by adhesions (Fig. 44). Sometimes

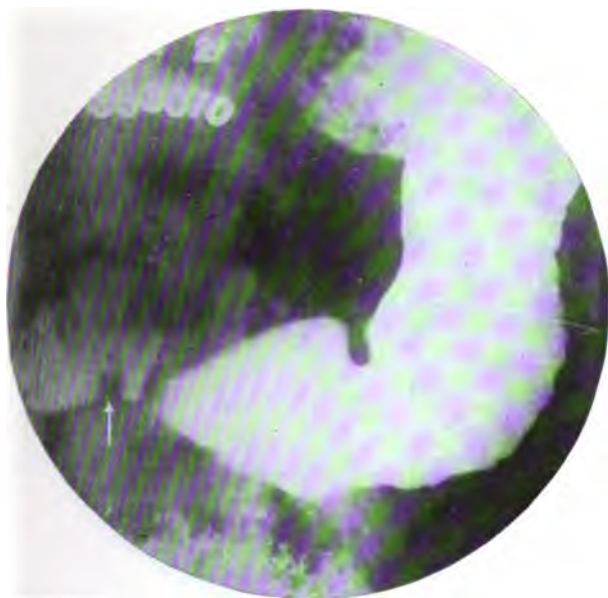


FIG. 44 (Case A363070).—Deformity of the duodenal bulb, associated with cholecystitis and adhesions. This deformity was diagnosed as duodenal ulcer.

this deformity is constant, cannot be distinguished from that of ulcer, and is responsible for a considerable proportion of errors. Åkerlund is of the opinion that the deformity they produce is often characterized by fine shallow irregularities, sometimes variable, and different from the typical defects caused by ulcer. I have not as yet observed any dependable differential features of adhesions. It is to be remembered also that adhesions may result from a perforated ulcer. Deformity of the bulb is not an inevitable effect of adhesions, as I have seen many patients in whom at operation the first part of the duodenum was

found to be embedded in adhesions although the bulbar contour was quite normal in appearance. Very rarely six-hour gastric retention and hyperperistalsis may result from obstructive pericholecystic adhesions.

Extrinsic tumors infringing on the bulbar contour are not common. They should usually be palpable and their presence thus be evident. The gallbladder sometimes makes a smoothly curved indentation in the bulb, but this is patently different from the irregular deformity caused by ulcer. Pressure against the spine may cause a bulbar filling defect. This can be eliminated by palpatory shifting during roentgenoscopy.



FIG. 45 (Case A59961).—Duodenitis with spastic bulbar deformity.

Benign tumors within the bulb are pathologic novelties. I have had one case in which the bulb contained a hemangioma. It appeared as a central filling defect in a large bulb of unbroken outline and the diagnosis of an intraduodenal tumor was obvious. Åkerlund has seen a few cases of papilloma with similar signs and only one was diagnosed as ulcer. I have observed one case, diagnosed by the aid of the roentgen ray as ulcer, in which the surgeon found a diverticulum on an angiomaticous base but could not determine whether an ulcer existed or not. In another instance a diverticulum was found opposite an ulcer which

had been diagnosed, but diverticula occur more commonly around the ampulla of Vater.

Judd has recently called attention to an eccentric form of ulcer which he calls the duodenitis type, or submucous ulcer. When excised the mucosal surface seems normal, but on close examination one or more pin-point ulcers are found, and the submucosa and muscularis are infiltrated. Spastic bulbar deformity is usually present in these cases just as in other types of ulcer (Fig. 45). Designating this type of ulcer has no bearing on clinical diagnosis or treatment, but in the

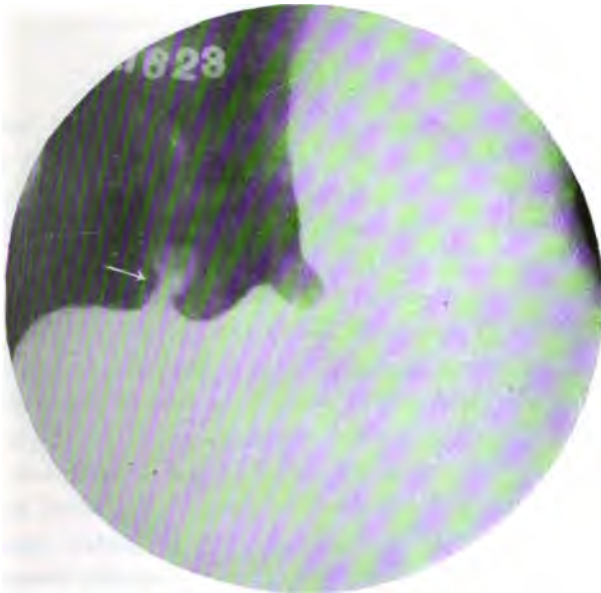


FIG. 46 (Case A321823).—Carcinoma of the pyloric end of the stomach and of the duodenum. Roentgen diagnosis: duodenal ulcer.

absence of induration and marked mucosal erosion a cautious surgeon might doubt the validity of the roentgen diagnosis. This consideration also applies to the occasional small ulcer which, after the abdomen is opened, shows no manifestations on the serosal surface, is not palpable, and is found only by incising the duodenum.

Cancer of the duodenum is among the rarities. Only five cases have been observed at the Clinic in its entire history. In none of the four cases examined by the roentgen ray was the growth mistaken for ulcer, and it was distal to the bulb in every instance.

Gastric lesions near the pylorus may be deceptive in various ways. Occasionally prepyloric cancer or ulcer does not visibly deform the antrum, and at the same time, if obstructive, gives rise to gastric retention and hyperperistalsis, or the lesion may produce deformity resembling a distorted bulb, and the examiner may be unable to determine the exact site of the pyloric ring (Fig. 46).

Error from stressing the subordinate signs of ulcer or being unduly influenced by the clinical history is scarcely excusable. Gastric hyper-tonus, hyperperistalsis (without retention), and hypermotility are not of themselves indicative of duodenal ulcer.

NEGATIVE ERRORS

Satisfactory roentgenoscopic examination requires attention to many technical details. If these are disregarded an ulcer may easily escape recognition on the screen. Two features are essential: the image must be clear, and the examiner's vision must be adapted to the relative darkness. To secure a clear image the milliamperage and voltage should be appropriate, the tube should have a focus as sharp as is consistent with reasonable endurance, the screen should be of the best quality, the patient should be close to the tube, and the diaphragm should be actively employed to narrow the field of observation.

In a case of cardiospasm the establishment of its diagnosis by the roentgen ray would seem to be sufficient, but I have been impressed by a few cases in which the condition was accompanied by duodenal ulcer. The relationship of duodenal ulcer to gastric spasm is well known and it is not unreasonable to suspect a similar connection with cardiospasm. At the Clinic we now request that after dilatation for cardiospasm the patient be returned for examination of the duodenum.

Occasional association of duodenal ulcer with gastric ulcer is a familiar fact. When the latter is found a careful search for a possible companion in the duodenum ordinarily should not be omitted. However, when the gastric ulcer is obviously of such character that perforation might result from manipulation, or when the patient is so weak that the examination is harassing, the examiner should be satisfied with the demonstration of the gastric ulcer alone (Fig. 47).

A duodenum which turns backward from the pylorus and is overlapped by the antral shadow in the anterior view is much more difficult to examine than the erect cap. In such instances the stomach is

usually of the steer-horn type, is swung more or less horizontally, and the pylorus lies well to the right. By turning the patient into the right oblique view, carrying it almost to the right lateral position if necessary, the cap can usually be seen.

It is a standard and safe rule that a duodenal bulb of normal outline negates the presence of ulcer. This is not absolutely true, for I have seen a few patients in whom the duodenal contour was apparently undeformed, but who at operation were found to have ulcer. Absence of spasm or minuteness of the ulcer may explain the lack of deformity.



FIG. 47 (Case A337234).—Concurrent gastric and duodenal ulcer. The gastric ulcer, the niche of which is seen at U, was diagnosed. The bulbar contour is normal.

I have noted exceptional instances in which even an extensive perforated ulcer failed to distort the bulb as seen by the roentgen ray. On the other hand, a small ulcer with active spasm may be detected readily. The surgeon is sometimes puzzled by these apparent inconsistencies of roentgen diagnosis.

A small minority of ulcers are located beyond the bulb in the second or third portion of the duodenum. In such instances the contour is not altered and if the distal duodenum is deformed it cannot be distinguished ordinarily by the roentgen ray from the irregular outline

produced by the *valvulae conniventes*. Unless stenosis results with its characteristic signs the roentgen ray will seldom discover the lesion.

SERIES OF CASES

To throw some light on the relative importance of each of these many sources of error I have canvassed our records for the twelve months ending June 30, 1921. During this period 522 cases in which a diagnosis of duodenal ulcer had been made by the roentgen ray went to operation. In 499 cases the ulcer was found by the surgeon; in twenty-three cases no ulcer could be demonstrated.

In eight of the twenty-three cases disease of the gallbladder or appendix or both was found. In none of these was the duodenum organically involved, and it may be argued that the bulbar deformity on which the roentgenologic diagnosis of ulcer was based was the result of spasm from the extrinsic lesions.

Adhesions around the duodenum were responsible for the wrong diagnosis in seven cases.

Five errors were due to prepyloric lesions, cancer in three cases, ulcer in two. All of these lesions were near the pylorus. A cancer involving the liver, but whose origin was not determined, may have been the cause of the duodenal deformity in one case, and in another the lesion was a cancer of the hepatic flexure.

Thus in twenty-two of the twenty-three cases there was definite justification for surgical intervention, and in two-thirds of them the lesion was in the right upper quadrant of the abdomen. In the remaining instance nothing could be found to explain the symptoms or diagnosis.

During the same period, of 544 cases in which a negative roentgen-ray diagnosis was made, 512 were confirmed by operation, and pathologic conditions other than ulcer were found. In the other thirty-two cases (5.9 per cent), a duodenal ulcer was discovered at operation, although its presence was not shown by the roentgen ray. Some of these negative errors had no reasonable excuse other than the inevitable fallibility of the examiner. In twelve of the cases the organic changes as described by the surgeon seemed adequate to produce deformity recognizable by the roentgen ray. The changes included various combinations of induration, scarring and contraction, and in three cases perforation had occurred. As I have stated, rather marked organic

alterations of the duodenal wall, even perforation, may exist without roentgenologic deformity, and possibly this was the case in some of the thirteen.

In eleven cases error was probably unavoidable. Eight of the ulcers were described as being small, 0.5 cm. or less in diameter, and in the absence of spastic distortion would hardly have been visible. In one case the ulcer was in the second portion of the duodenum, 6 or 8 cm. from the pylorus.

In the remaining nine cases duodenal ulcer coexisted with gastric ulcer. In eight of these the examiner discovered the gastric ulcer, but either failed to observe any evidence of the duodenal ulcer, or did not look for it. Roentgenograms preserved in two of the eight cases show a normal bulbar contour. In the ninth case neither the gastric nor the duodenal ulcer was found by the roentgen ray. The gastric ulcer was small and on the posterior wall, but the duodenal ulcer was of the puckered type and should have been discovered.

SUMMARY

The principal causes of affirmative error in the diagnosis of duodenal ulcer in the order of their importance are reflex spasm, periduodenal adhesions, and gastric lesions near the pylorus.

Duodenal spasm from extrinsic causes is most often associated with cholecystitis or chronic appendicitis.

Juxtapyloric gastric lesions may implicate the duodenal bulb or alter landmarks so that exact diagnosis may be difficult.

Tumors of the duodenum, either benign or malignant, and diverticula are rare sources of error.

Confusion of the bulbar shadow with that of other parts of the duodenum or with the shadows of adjacent concretions is a technical fault which can usually be avoided.

The percentage of negative errors in this series slightly exceeds the percentage of affirmative mistakes. Many of these diagnostic failures are explainable by the absence of bulbar deformity, either organic or spastic.

Failure to diagnose a duodenal ulcer associated with a demonstrable gastric ulcer is not a grave oversight.

Ulcers situated beyond the bulb can hardly be diagnosed as such, although obstruction may be demonstrable. They constitute a very small percentage of the total.

Many negative errors are avoidable. Some of them are due to technical faults, others are solely the result of careless observation and are indefensible. Perfection is admittedly unattainable, but the roentgenologist should not criticize himself too charitably.

In all that has been said there has been no intention to furnish an alibi for roentgenologic mistakes. On the contrary, although the mistakes of the roentgen ray in the diagnosis of duodenal ulcer are relatively few, it is to be hoped that they can be further reduced. Assuming that examination is thorough and careful, the affirmative mistakes seem difficult to attack. Negative errors can doubtless be further lessened by technical precision and closer observation, so that fewer cases with actual bulbar deformity will pass unnoted.

When one considers that the affirmative errors in this series amounted to only 4.4 per cent, and how difficult or impossible it is to diagnose the presence of adhesions or spasm due to extrinsic lesions, the wisest procedure for the roentgenologist is to diagnose duodenal ulcer when a definite, persistent deformity of the bulb is seen. The visualization of a well-filled bulb, regular in outline, can mean nothing but a normal duodenum from a roentgenologic standpoint.

Finally, the question arises of supplementing the roentgenologic findings with the clinical data in order to make a correlated diagnosis and avoid occasional mistakes. However helpful the clinical facts may have been in the developmental stage of gastric roentgenology and however necessary they still may be for the interpretation of other roentgenologic findings, I believe that their employment at this time by the roentgenologist in the diagnosis of duodenal ulcer is unnecessary and would increase rather than diminish his mistakes. While the typical anamnesis of ulcer is admirably simple and clear, it is not pathognomonic, nor is ulcer always accompanied by a characteristic history.

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EXCISION OF ULCER OF THE DUODENUM*

E. STARR JUDD

The immediate and ultimate results of gastrojejunostomy performed for ulcer of the duodenum are very satisfactory. Two considerations are essential to these good results. First, the operation must be decided on after the ulcer has been demonstrated, and second, the mechanical arrangement of the stomach and intestine and the technic for joining the two must follow the plans made by surgeons with the widest experience.

In view of the fact that there is so much evidence to support the belief that ulcers in the duodenum may be the result of extension of infection from some focus in the abdomen, or more remote point, it is necessary that such coexisting infection should be cared for at the time of the operation on the stomach or very soon after. Certain regulations of diet following gastro-enterostomy are undoubtedly essential. Indiscretions soon after the operation have often been followed by a return of the former symptoms, and have seemed to play a part in the formation of secondary ulcers.

Gastro-enterostomy does more than effect symptomatic relief. It has been said by some observers that all ulcers of the duodenum heal after the gastro-enterostomy, I find it difficult to decide just what effect gastro-enterostomy has on the ulcer. However, in our cases in which secondary operations were performed at various times, subsequent to the gastro-enterostomy for ulcer, there was always evidence of the ulcer in the form of scar and induration. Just when the ulcer may be termed healed, I believe, will depend on when all of the ulcerated area has been replaced by scar tissue. Perforation of the ulcer is a common occurrence, and yet, so far as I have been able to learn, such perforation practically never occurs after gastro-enterostomy. I know of only one authentic case (personal communication from Moynihan). This suggests that if the gastro-enterostomy did not effect a definite change in the ulcer itself, perforation would occur more often. On the other

* Presented before the Western Surgical Association, St. Louis, December, 1921. Reprinted from the Transactions of the Western Surgical Association, 1921.

hand, it is well known that if an ulcer of the duodenum has caused severe bleeding, a return of the hemorrhage may be looked for in a definite percentage of cases (about 12 per cent) after gastro-enterostomy. The hemorrhage may come several years after the operation; furthermore, it may come when the patient has been completely relieved of his dyspepsia. The phenomenon indicates that the ulcers do not all heal completely as a result of gastro-enterostomy.

Careful macroscopic and microscopic study of the tissues has proved that inflammatory lesions of the duodenum occur in two distinct types, one, the true ulcer, and one more distinctly inflammatory, probably better designated duodenitis. We might assume that the duodenitis type of ulcer is the healed true ulcer, but I believe that it is a separate lesion and never has been and never will be a true ulcer. The first type is the true ulcer, and is in every way similar to an ulcer in the stomach. There is definite congestion and stippling of the peritoneal coat and the induration is usually rather extensive so that the lesion can be palpated and recognized as an ulcer with a crater. The second type is more markedly congested and stippled than the true ulcer; usually there is very little if any induration in the tissues. In many cases the palpation of this lesion does not differ from palpation of the normal duodenum. On excising the area, instead of a crater as in the first type, the entire surface of the mucous membrane is found to be covered with normal mucosa; the condition might be called a healed ulcer if it were not producing symptoms. The thickness of the ulcerated area of the duodenum is very little if any greater than that of the normal wall of the duodenum. If the surface of the mucous membrane is examined closely it may be found to contain one or more pin-point ulcers and scar tissue. Both the submucosa and muscularis are usually infiltrated with round cells and this infiltration may extend some distance into the tissues of the intestinal wall. Histologically this ulcer is similar to the submucous ulcer sometimes found in the urinary bladder. Clinically, there seems to be little difference between the two types. The histories in our cases of duodenitis indicate that this type of ulceration is not a stage from which true ulceration later develops. The duration of symptoms average the same as in cases of true ulcer. The shadow of the deformity of the duodenal cap in the roentgenogram produced by the two forms of ulceration is the same except that the niche which represents the crater of the ulcer, while often seen in the ulcer type, is absent in duodenitis.

The designation of these two types of ulceration of the duodenum has no bearing on the diagnosis or treatment, but is of interest from the pathologic point of view, and may offer some suggestions with regard to etiology. Formerly I believed that hemorrhage was a rare occurrence in cases of duodenitis, but recently I have had reason to believe that very severe hemorrhages may occur in these cases. In the past few months I have seen several patients who had hemorrhages so severe that they were almost exsanguinated, and yet the lesion in the duodenum was in the form of duodenitis rather than of true ulcer. In some of the cases the area of the inflammation extended throughout the entire circumference of the duodenum, and yet there was no demonstrable ulceration of the mucous membrane.

In view of the fact that gastro-enterostomy, when properly selected and performed, has offered such exceedingly good results in the treatment of duodenal ulcer it seems best to continue to use the procedure in most cases. Whether a good result from gastro-enterostomy may be expected before the ulcer has produced obstruction has been widely discussed. At one time it was thought best to produce an obstruction by pyloric exclusion in the cases in which the pylorus or duodenum was not obstructed. It was often said that a gastro-enterostomy would not functionate properly if the pylorus was open. This statement is seldom heard now, and so far as I know pyloric occlusion has practically been abandoned as an unnecessary procedure. Undoubtedly, there is a certain amount of true mechanical obstruction, or at least spasmodic obstruction, produced by most ulcers, and I believe that we have overemphasized the importance of this phenomenon in obtaining good results.

In spite of generally good results from this type of operation there are certain cases in which it seems well to excise the ulcer in preference to making a gastro-enterostomy. It is this group of cases which I shall discuss particularly at this time. While we have performed several different types of plastic operations on the pylorus, in the cases in this group operation was not performed on the pylorus or stomach.

Roeder has recently reported an operation similar to the one I shall describe, although the indications for the operation and the technic are somewhat different. Finsterer reported a series of thirty-five cases of severely bleeding ulcers of the duodenum in which operation was performed while the hemorrhage was severest. Finsterer believes that it

is better to remove the ulcer at this stage than to postpone removal until the severe anemia is overcome, as has been the custom recently.

Nowak, assistant in von Eiselsberg's clinic, has reported a series of forty-seven cases of duodenal resection for ulcer of the duodenum. He believes that resection is applicable in the great majority of cases, but says that the indication for the operation should depend on the general condition of the patient and on the proximity of the common and pancreatic ducts. He believes that with good technic the danger and mortality from the operation are scarcely greater than with other indirect methods. This operation is much more radical than the one I have performed.

The excision of the duodenal ulcer or ulcers and the reconstruction of the duodenum is accomplished as simply as possible. The symptoms of which the patient complains are the result of these ulcerations, and to obliterate them it is only necessary to remove the lesion. This is the fundamental principle of the operation; it does not change the physiology of the stomach. If, owing to the lesion in the duodenum, such change has occurred, then the organ should return to normal by the removal of the lesion. The question has been asked, "What will prevent other ulcers from forming?" A better knowledge of the cause of the original ulcer is necessary in order to answer this question. All foci of infection should be cleared up. If the ulcer has formed as a result of infection, the source of trouble will have been eliminated. I am not making a plea for excision of the ulcer; on the contrary, I am convinced that the operation has its limitations. Quite as good results will be obtained in selected cases as can be secured by any form of pyloroplasty, or by gastro-enterostomy, and with a little less risk to the patient. The normal anatomic and physiologic relationship of the stomach, duodenum, and jejunum will be preserved.

The excision of ulcer is particularly indicated if the entire ulcer can be excised and the duodenal lumen maintained, and if the entire operation can be performed more easily than gastro-enterostomy. If the ulcer is of the type that bleeds during an attack, excision is preferable. If localized pain is one of the chief symptoms and dyspepsia is slight or absent, I believe it is better to excise the ulcer if it can be done readily. If the gastric acids are not high, and especially if the patient has a tendency to neurasthenia, it is best to excise the ulcer rather than to perform gastro-enterostomy.

Ulcers of the duodenum should not be excised unless the technical

steps of the operation can be performed satisfactorily. This will be possible only if the duodenum is mobile or easily mobilized. It is true that if the duodenal lumen is interfered with, gastrojejunostomy may be made; on the other hand, if it is necessary to make a gastrojejunostomy, it is ordinarily not necessary to remove the duodenal ulcer; therefore, the gastrojejunostomy should be performed primarily.

In the operation which I am describing the ulcer is excised without attempting to enlarge the pylorus. We have had satisfactory results from the Finney pyloroplasty and also from the Heinecke-Mikulicz operation, but our present technic is more easily carried out than the others and we believe affords better opportunity to remove all of the ulcerated tissue. This operation is based on the belief that the ulcer is the cause of the symptoms and that its removal will be all that is necessary for complete relief.

TECHNIC OF OPERATION

The incision into the duodenum is made transversely on a line parallel with the ring fibers of the pylorus (Fig. 48). The upper transverse incision is usually placed just below the pyloric muscle, and the lower one far enough below the ulcerated area to pass through good tissue. After the ulcerated area has been removed the entire surface of the mucous membrane of the duodenum and pyloric end of the stomach are exposed for inspection. We have been rather surprised to find multiple ulcers in a large number of cases; contact ulcers are much more common than we had believed, and ulcers on the posterior wall some distance from the pylorus have been unexpectedly encountered in several instances. In some of the cases of multiple ulcers it has seemed best to cauterize and suture over the deep ulcers (Figs. 49 and 50). In most cases we are able to destroy all of the ulcers and finish with a good duodenum. After suturing over the deep ulcers the opening on the anterior surface is closed by three layers of sutures (Fig. 51), thus the pyloric end of the stomach is sutured to the anterior surface of the duodenum, which almost amounts to a gastroduodenostomy. The entire duodenal cap is destroyed, so that a roentgenogram made after the operation reveals much the same deformity as that produced by the ulcer. This point must be kept in mind in making postoperative roentgen-ray examinations.

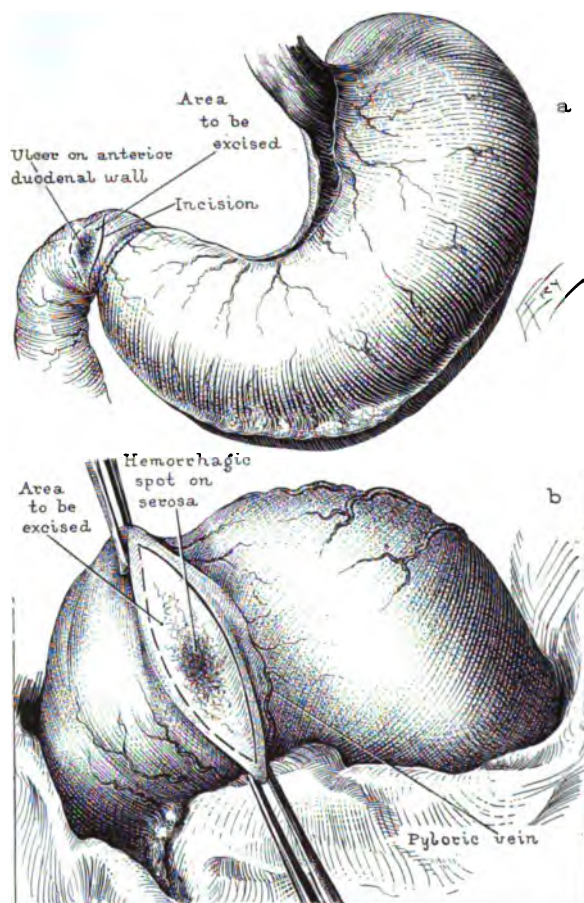


FIG. 48.—a. Position of incision in duodenum. b. Duodenum held by stomach clickers to facilitate making of incision.

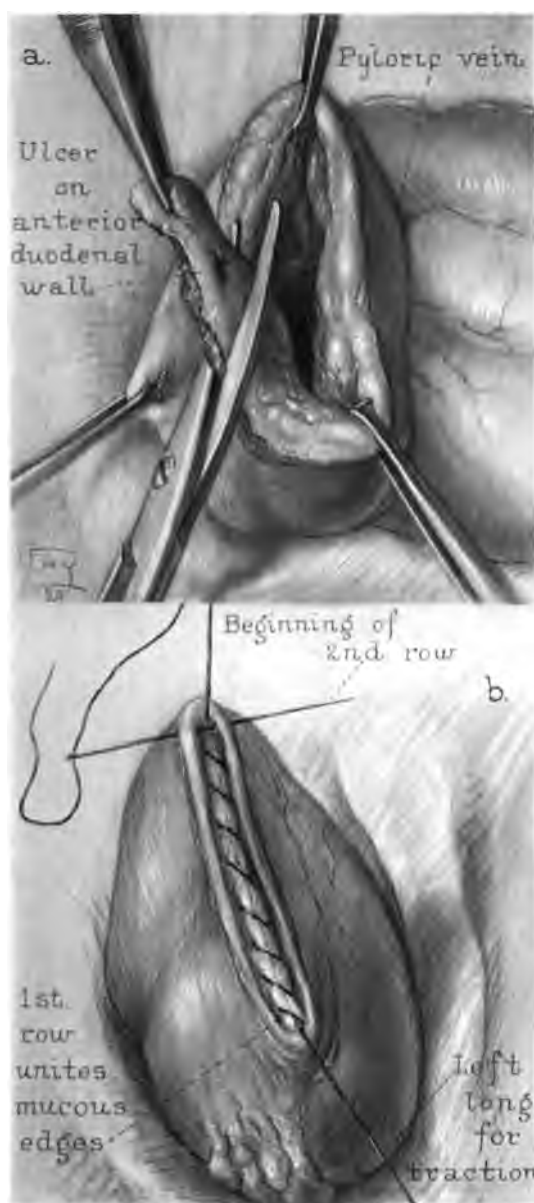


FIG. 49.—a. Excising ulcer on anterior duodenal wall. b. Mucous coat sutured with catgut.

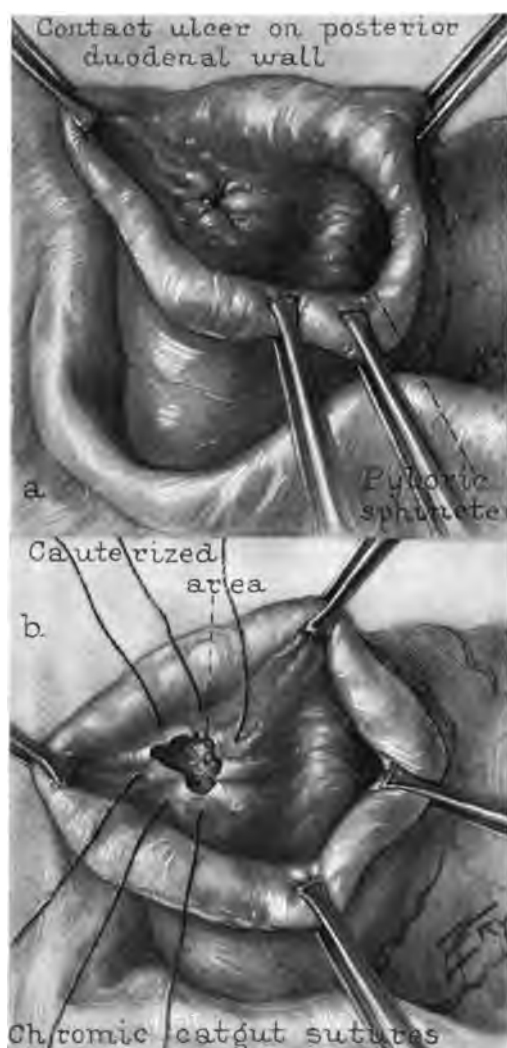


FIG. 50.—a. Duodenum held open to expose contact ulcer. b. Cauterized area on posterior duodenal wall ready to be closed.



FIG. 51.—a. Beginning of last suture. b. Suture completed.

RESULTS OF OPERATION

The operation has been performed in 141 cases in the Clinic with satisfactory results. The immediate results are very gratifying and the convalescence is easier than after almost any other operation on the stomach. There is no vomiting and apparently the stomach empties itself at once. In one or two cases there was some evidence of oozing, as shown by the tarry stools. This, however, was of no consequence. There was one death in the series; an elderly woman developed pneumonia and died on the tenth day.

In most of the cases the functional result was very good. Gastric analyses were made a week or ten days after the operation in practically all of the cases, and repeated examinations were made in some. Following gastro-enterostomy, of course, the content of the stomach was not acid, and after excision of the ulcer there was a marked reduction in acid, although it was never entirely absent. In a few cases the acidity was not materially reduced. In most cases the acids were normal a few weeks after the operation.

In two cases I made gastro-enterostomies secondary to the excision of the ulcer. One of the patients had a new ulceration with return of symptoms two years after the first operation, and one, a rather nervous girl, did not obtain complete relief. In this case I was unable to determine that there was any ulceration, and the lumen of the duodenum was apparently normal. In one case a gastro-enterostomy was performed elsewhere some months later because the gastric acids had remained too high after the excision of the ulcer, and relief of symptoms was incomplete. The acids still remained high after the gastro-enterostomy.* An average of analyses of gastric contents in twenty-five cases showed, before operation, total acids 54 and free hydrochloric acid 41; eight days after operation it was total acids 34 and free hydrochloric acid 19. During this time these patients were on hospital diet.

COMMENT

I performed this operation a number of years ago in cases in which gastro-enterostomy had been unsatisfactory because of the formation of a jejunal ulcer. We soon learned that the best procedure in the jejunal ulcer cases is to undo the gastro-enterostomy and excise the original ulcer. The operation was so satisfactory in these cases that

* I am indebted to Dr. E. L. Tuohy of Duluth for the follow-up notes in this case.

we employed it in others in which the indications seemed suitable. I am convinced that the excision of duodenal ulcer will never become general or take the place of gastro-enterostomy.

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FOCAL INFECTION AND ELECTIVE LOCALIZATION OF BACTERIA IN APPENDICITIS, ULCER OF THE STOMACH, CHOLECYSTITIS, AND PANCREATITIS*

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Infections in organs or tissues remote from the surface of the body, such as joints, bones, and endocardium, are conceded by all to be hematogenous in origin. The origin of disease in organs directly or indirectly connected with the surface of the body, such as the stomach, gallbladder, pancreas, and appendix, is still considered by many to be due in the main to direct infection through the mucous membrane lining the intestinal tract or the ducts which drain into it. Many facts suggest that in these too the infection may be blood born. The lesions in the early stages or milder forms of infection in these structures are often sharply circumscribed, hemorrhagic, and situated in the mucosa, submucosa, or peritoneal coat, with no evidence of a diffuse involvement of the mucous membrane. The fact that the changes in pancreatitis are usually more marked in the head of the pancreas is quite generally considered evidence of an ascending infection through the ducts. But this does not follow, since I have found that the same is true in pancreatitis from the intravenous injection of bacteria having affinity for this organ.

Experiments to produce ulcer of the stomach by feeding bacteria have been unsuccessful except in starving animals. In my¹⁷ work ulcer of the stomach could not be produced even when streptococci, proved to produce ulcer on intravenous injection, were fed in large quantities. The addition of sharp particles to the diet containing the streptococci was also of no avail.

Streptococci, proved to have an affinity for the gallbladder when injected intravenously, failed to produce cholecystitis when injected directly into the lumen of the gallbladder.¹⁸

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Intravenous injection of streptococci, and in some instances of colon bacilli, from acute appendicitis has been followed by marked localization and lesions of the appendix of rabbits,¹⁹ whereas attempts to produce appendicitis by way of the mucous membrane have been unsuccessful unless the blood supply is markedly interfered with.

From these facts and many others it is certain that the normal mucous membrane of the intestinal tract affords marked protection against invasion of the bacteria usually found in ulcer of the stomach, cholecystitis, and appendicitis. A break in continuity or increased permeability of the lining cells from trauma, or otherwise, appears necessary for local invasion, whereas in hematogenous infections the bacteria appear to gain entrance into the blood stream chiefly through a chronic localized focus of infection.

The place of localization of bacteria after entrance into the blood stream, aside from the well known factor of trauma, or the *locus minoris resistentiae*, has been considered as more or less accidental. Many facts indicate that this is not the rule and that delicately balanced conditions must prevail before localization and growth of bacteria can occur in a given tissue. The blood stream is invaded by the typhoid bacillus in typhoid fever, yet the lesions are limited to Peyer's patches and other lymphoid structures in the intestinal tract. The pneumococcus enters the blood in practically all cases of lobar pneumonia, yet localization remains limited to the lungs and pleura. The *Streptococcus viridans* has been isolated from the blood daily for weeks and even months in chronic septic endocarditis, but localization remains limited to the endocardium. The lodgment of even millions of these streptococci, as occurs in emboli, from the vegetations is not sufficient to insure continued growth in tissue other than the heart valves.

In the infectious diseases the properties of specific microorganisms determine their localization. The idea that localization may be determined by peculiar properties in different strains of the same species of bacteria, or of even the same strain when subjected to different conditions, had its origin in my experiments some years ago in which changes suggesting true mutations were induced in the pneumococcus-streptococcus group of organism.¹⁵ The idea was placed on substantial ground when the *Streptococcus viridans* from endocarditis and other strains of streptococci of low virulency were passed successively through animals. The localization following intravenous injection changed as the infecting power increased. At first hemorrhages in the heart valves and endo-

carditis were the chief findings. Later lesions in and around joints, in muscles, especially the tendinous end, and eyes, especially iritis, developed. Still later lesions of the kidneys and of the stomach developed, and finally, as the virulency became high, death occurred from invasion of the blood stream without focal lesions.

The findings in the stomach were particularly instructive.¹⁶ The hemorrhages and ulcerations were found to be due to localized infection. The ulcers were often single and deep, and showed, as those in man, marked tendency to hemorrhage and perforation. Generalized infection did not occur. The theory that the usual type of gastric ulcer may be due to streptococci was proposed at that time. The supposed relation between infected tonsils or teeth and gastric ulcer was, in the light of the experiments, considered to be due not to the swallowing of bacteria, as is usually supposed, but to the entrance into the blood of streptococci of the proper kind of virulence to produce local infection in the wall of the stomach. It was through these experiments that the idea of the elective localization of bacteria took definite form, and I have since studied the pathogenesis of various diseases from this standpoint.

The cultures from excised tissues and from foci of infection have been made by special methods which offered a gradient of oxygen tension, a point not sufficiently considered by some workers along this line. The localizing powers of the freshly isolated strains of the bacteria isolated from the tissues, and, owing to the work of Billings on focal infection, those from the focus as well, have been measured by intravenous injection in animals. The results obtained have been published from time to time, and for details reference should be made to the original reports. In this paper I wish to review briefly the results obtained in the earlier work in ulcer of the stomach, cholecystitis, and appendicitis, diseases of especial interest to surgeons, and to record further studies along similar lines.

RESULTS IN THE EARLIER STUDIES

Streptococci were found to be the most important organism in the tissues in each of these diseases. They were chiefly of the nonhemolytic type, of a low grade of virulence, and culturally much alike. Wide differences in inherent properties, however, became apparent on intravenous injection. The streptococci tended to localize and produce

lesions in organs corresponding to those in the diseased persons from whom they were isolated. This was true of the strains from tissues as well as of those from infected tonsils or other foci of infection. Thus 68 per cent of sixty-eight animals injected with fourteen strains from appendicitis developed hemorrhagic lesions of the appendix¹⁹; 60 per cent of 103 animals injected with eighteen strains from ulcer showed hemorrhage and ulcer of the stomach¹⁷; and 80 per cent of forty-one animals injected with twelve strains from cholecystitis developed lesions in the gallbladder.¹⁸ This was in sharp contrast to the incidence of lesions in these organs (3 per cent, 17 per cent, and 4 per cent respectively) following injection of forty-four animals with thirty-four strains of streptococci from miscellaneous sources. The lesions which developed in the respective specific organs were not only more common, but were often more marked when lesions in other organs were slight or absent. Moreover, the strains from acute ulcer, cholecystitis, and especially appendicitis, produced lesions more marked than those from the chronic forms of these conditions.

The demonstration that streptococci in infected tonsils and teeth may have elective localizing power placed these so-called harmless infections, teeming with bacteria, in the front rank in importance as sources of hematogenous infections. Corroborative clinical evidence indicating causal relationship between the focus of infection and systemic disease is not lacking. The foci are present in demonstrable form in a high percentage of patients with the diseases under consideration. Acute attacks often follow exacerbations of infections in sinuses, tonsils, and teeth. Evans has noted a marked increase in the incidence of appendicitis during epidemics of sore throat. The average time that elapsed between the respiratory infection and the onset of appendicitis was sixteen days.⁶ The presence of streptococci having elective affinity for the appendix has been demonstrated in the tonsils at the time of acute appendicitis following tonsillitis, and their absence as recovery ensued.¹⁹ This I have shown also in cases of ulcer following acute infection in tonsils and sinuses,¹⁷ a fact in strict accord with the increased incidence of symptoms in ulcer during the months when these infections are prevalent, as first noted by Moynihan. Metastatic infection in other parts, such as the joints and the endocardium, commonly occur, not at the height of the nasal and tonsillar infection, but some time later. It appears that the bacteria acquire elective localizing power in the focus and that the various diseases may be manifestations

of phases in the infecting power of the same microörganism. The symptoms in the systemic condition often improve when foci of infection are removed unless mechanical factors have come to play an important part in their production. However, not too much value should be attached to purely clinical observations on this point. It is very difficult to know at a given time whether a suspected primary focus is responsible, whether other foci exist in inaccessible parts, whether a previous removal of a focus had been thorough, especially if in the dental area, whether the foci removed actually harbored the bacteria with which the disease could be reproduced, and finally whether in a given case, especially if chronic, the infection has not become so thoroughly established as to tend to progress independently of the focus.

My original experimental studies in ulcer,¹⁷ cholecystitis,¹⁸ and appendicitis¹⁹ extended over a short period, and included a relatively small series of cases. The results were, on the whole, contrary to current opinion, especially in ulcer. Some investigators have had difficulty in corroborating my findings. The number of bacteria injected was relatively large, and this has been objected to. I believed it worth while, therefore, to continue the studies in a larger and more varied series, including recurrent ulcer, and to test the effect of the injection of smaller doses of bacteria. This has been done as occasion developed during the past five years. The method of study has been similar to that in the earlier work. In all the cases the symptoms were active at the time of the study and in all there were foci in which a causal relationship was suspected. Painsstaking effort was made to obtain cultures from the depths of the focus and to eliminate as far as possible the more saprophytic bacteria on the surface. Glucose-brain broth in tall columns was substituted for ascites-glucose broth. The dose for a routine injection consisted of from 0.1 to 0.25 c.c. for each 100 gm. of body weight. Usually only one injection was given. In order to rule out all possible objections to dosage the small amount of pus expressed from tonsils and emulsions of tonsils was injected directly. The primary culture in glucose broth was usually injected and the identity of the causative organism determined by plating the culture, by making cultures of the tissues showing lesions, and by making control cultures of the blood and normal mucous membrane of the stomach and other organs showing no lesions.

RESULTS IN UNPUBLISHED EXPERIMENTS

In the series sixty-five animals (fifty-nine rabbits, four dogs, and two guinea-pigs) were injected intravenously with the cultures from nineteen cases of ulcer of the stomach or of the duodenum. Thirty-two of these were injected with cultures from the tonsils, six with the bacteria in the pus from the tonsils, seven with the streptococci isolated from three excised ulcers, and twenty-three with the cultures from infected teeth. The incidence of lesions in the stomach and in the duodenum was about equally high in each of these groups. Hemorrhage or ulcer, or both, developed in fifty-two (80 per cent) of the animals injected. The lesions in other organs were either wholly absent or relatively slight. Fifteen animals showed lesions in the gallbladder besides those in the stomach, seven showed a few lesions in the skeletal muscles, five, in the joints, one each, in the kidney and the urinary bladder, and nine, hemorrhages in the heart valves. The lesions in the stomach consisted first of areas of hemorrhage varying greatly in size and shape, and later of one or more ulcers. The ulcers were usually situated along the lesser curvature and the pyloric end. Ulceration usually occurred first in the center of the hemorrhagic areas and extended to the submucosa or muscularis. In some instances the ulcer formed in circumscribed, grayish, swollen, necrotic areas free from hemorrhage. The base at first was hemorrhagic, but later became clean and free from necrotic tissue. Usually there was no infiltration or hyperemia of the overlying peritoneum.

All the six animals injected with the bacteria which had grown in the tonsil developed striking lesions in the stomach or duodenum. Three of these did not have lesions elsewhere, and three had hemorrhage of the tricuspid valve in addition, but no other lesions. Only four animals died from the effects of the injection, two in one day, and two in two days. The rest appeared well when anesthetized, usually in from two to three days after the last injection. The streptococcus was found in the blood in all the animals that died, but it was found in only three of thirty-one that were anesthetized and in which the blood was cultured. Cultures were made of the excised areas of hemorrhage or ulcers in seventeen animals. Of these, fifteen yielded the streptococcus, and two were sterile. Control cultures were made of the normal mucous membrane of the stomach, the liver, the spleen, the kidneys, and the brain in twelve animals showing ulcer. These and

the blood were sterile or showed relatively few streptococci compared with the number isolated from the lesions in the stomach.

Since my last report on ulcer, tissue cultures have been made from twenty-seven chronic ulcers excised at operation. Streptococci were isolated in eighteen, colon bacilli in five, staphylococci in six, and six showed no growth. In all of the latter healing was well advanced. Control cultures were made of the tissues in carcinomatous ulcers from eleven patients. In these streptococci were found in only two, colon bacilli in five, and staphylococci and Welch bacilli in two each.

The history of ulcer symptoms in the cases studied ranged from six months to twenty-one years. The ages of the patients ranged from twenty-seven to fifty-three years. All had active symptoms at the time of study, and two had had gastric hemorrhages a short time previously. Only four had a history of attacks of tonsillitis; two of these had arthritis in addition to ulcer. In none were the tonsils acutely inflamed; most of them were small and contained a large pocket at the pole from which pus could be expressed. The cultures from dental foci were chiefly from infected areas in the apical region of devitalized teeth. The size of the areas of rarefaction around the teeth varied greatly. In some it was slight, in others marked. All were symptomless. In no instance did these areas contain visible pus, and none communicated with the surface through a sinus. Tonsillectomy was advised and performed in four cases because of the striking localization of the streptococci in the stomach of the animals. Improvement in ulcer symptoms followed in each patient. In three cases elective localization occurred with streptococci both from the tonsils and the teeth, and in two with the streptococcus from the tonsils and from the ulcer. No localization followed intravenous injection of the streptococcus from the focus in two cases, nor from the excised ulcer in one case.

SUMMARY OF RESULTS IN ILLUSTRATIVE CASES

There were two cases of ulcer in the series in which the cultures had affinity for the mucous membrane of the stomach and for the mucous membrane of the gallbladder. The relatively high incidence (21 per cent) of lesions in the gallbladder, shown in Table 1, is due in large part to these two cases. In one of these a chronic indurated ulcer of the lesser curvature of the stomach was excised, and a distinctly thickened and hyperemic gallbladder, with swollen glands, was found. The

patient made a good recovery from ulcer symptoms, but subsequently developed typical attacks of cholecystitis. The streptococcus from the tonsil as isolated, and after one and two animal passages, was injected into six animals, five rabbits and one dog. Marked lesions in the stomach or duodenum developed in all, and two showed lesions of the gallbladder in addition. The other case had a perforating ulcer of the duodenum without evident lesions of the gallbladder. The streptococcus from the tonsils was injected into nineteen animals. Fifteen received a pure culture in the first, second, and third animal passages, two a mixture of the streptococcus and colon bacillus in the primary culture from the tonsils, and two the mixture of bacteria in the pus directly from the tonsils. Fourteen (74 per cent) showed hemorrhages or ulcer of the stomach or duodenum, nine showed lesions of the gallbladder in addition, and four showed cholecystitis only. The lesions in other organs were few. Two showed hemorrhages in the heart valves, one slight arthritis, and one a few lesions of the kidneys.

Five rabbits were injected with the colon bacillus in the second and third animal passages. All developed cholecystitis, and three slight hemorrhages in the stomach or in the stomach and duodenum. One additional rabbit injected with the strain in the fourth passage died of overwhelming infection without developing focal lesions anywhere.

Localization in the stomach and duodenum was in general the striking picture following the injection of the streptococcus. The lesions in the gallbladder were relatively slight and consisted usually of localized necrotic areas surrounded by hyperemia and infiltration, but marked diffuse edema with fibrinous exudate did not occur following injection of the streptococcus alone. Following the injection of the colon bacillus the picture was reversed. The lesions in the stomach were slight, while those in the gallbladder were marked. The most marked lesions in the gallbladder, however, occurred when a mixture of the streptococcus and colon bacillus was injected.

We have had the rare opportunity to study the elective localizing power of the bacteria from infected teeth in a man who had recurring attacks of ulcer with hemorrhage, and on whom a gastro-enterostomy had been performed twelve years before. No attention was paid to the question of foci of infection at that time. After the surgical removal of five infected teeth the patient's symptoms gradually disappeared under medical management, although heretofore his condition had been refractory to this treatment. The streptococci from the gran-

ulomas of three teeth and from one devitalized tooth which showed no granuloma were injected into four rabbits. The animals appeared well forty-eight hours later, when anesthetized. All showed hemorrhages and ulcer of the stomach. The ulcers were situated along the lesser curvature and in the pylorus. Three of the four rabbits showed hemorrhage and edema opposite the roots of the lower incisors. No other lesions had developed.

The results of the animal experiments performed in connection with a patient having symptoms of chronic cholecystitis without stone, and chronic pancreatitis with achlorhydria, representing the type described by W. J. Mayo, emphasize still further the importance of studies of focal infection and elective localization. This patient complained of distress after eating, repeated attacks of moderately severe pain in the regions of the gallbladder and pancreas, of recurring attacks of diarrhea, and marked loss in weight (60 pounds). A general examination was negative except for slight tenderness in the right hypochondrium. Two devitalized abscessed teeth were found and removed, and one abscess in the upper jaw where a tooth had been extracted years before was drained. The patient continued to lose weight. Six months later the tonsils were removed. Following tonsillectomy gradual improvement occurred. The distress after meals, the attacks in the region of the gallbladder, and the attacks of diarrhea disappeared, and the patient regained health and most of her former weight.

The primary culture from the tonsil was injected into one rabbit and three dogs. One of the dogs died in twenty-four hours; the other two and the rabbit were chloroformed in forty-eight hours. The picture was most striking. All four animals showed lesions of gallbladder, pancreas, and stomach. The gallbladder and pancreas were hemorrhagic and edematous. The lesions in the pancreas were more marked in the head. The stomachs appeared very different from stomachs following injection of the ulcer strains. The acid-secreting portion of each was extremely hyperemic and showed numerous fine superficial hemorrhages, while the pyloric end was normal. The streptococcus isolated from the edematous fluid surrounding the pancreas in one of the dogs was then injected into a dog and into a pregnant cat. Marked lesions of the gallbladder and pancreas developed in both, but the stomach in each was spared. The cat aborted and the one nearly full grown fetus available for examination showed hemorrhagic fluid in the peritoneal cavity, and marked edema and small hemorrhages of the

pancreas. Cultures from the lesions in the pancreas of the fetus, of the pancreas and gallbladder in the mother cat, and of the pancreas and gallbladder in the dog yielded the streptococcus injected.

About one year after tonsillectomy the patient again began to lose weight and strength. At this time three encapsulated roots of teeth were found and removed surgically. Cultures of two yielded green-producing streptococci; the other was sterile. Injection again showed similar localizing power, and with the removal of these foci the patient again improved.

During the course of the five years, careful necropsy records have been kept of the lesions found after intravenous injection of cultures from tonsils, and so forth, in diseases other than ulcer in which elective localization was not obtained, as well as in normal individuals. These have been compiled to serve as control experiments. Of a total of 212 animals injected with seventy-one strains only twenty (9 per cent) revealed significant hemorrhages or ulcer of the stomach or duodenum. This low incidence was not due to a lower general virulence of the streptococci injected because in this series the total mortality was nearly five times as high as in the ulcer series. The incidence of lesions in organs other than those in the stomach or duodenum was higher and the lesions occurred in a larger number of organs. The muscles, joints, and kidneys ranked highest, the incidence being 12, 9, and 9 per cent respectively (Table 1).

Among the diseases studied in the miscellaneous group were acute myelogenous leukemia, urticaria, ulcerative colitis, bronchitis, elephantiasis, thyroiditis, diabetes, purpura, jaundice, epididymitis, acute pyorrhea, dermatitis, and angina pectoris. Many of the cultures injected were obtained from tonsils or teeth of persons who were well at the time of the experiments. Moreover, an additional check on these experiments is given by the low incidence of lesions in the stomach and duodenum following injection of streptococci from other diseases in which elective localization was demonstrated. Thus lesions in the stomach and in the duodenum developed in only 13 per cent of 123 animals injected with cultures from twenty-two cases of acute epidemic poliomyelitis, in 6 per cent of eighteen animals injected with cultures from the tonsils in four cases of neuralgia, and in 14 per cent of 159 animals injected with streptococci from twenty-four cases of myositis (Table 1).

In Table 1 is given a complete summary of the localization of strep-

tococci obtained from ulcer, cholecystitis, and appendicitis, and, as controls, localization of streptococci from myositis, from acute poliomyelitis, and from miscellaneous sources. The incidence of lesions in the various organs is given in percentages so that the figures are directly comparable.

DISCUSSION AND SUMMARY

In view of the large number of animals injected and the wide range of the source of the streptococci, the incidence of lesions in the various organs following injection of nonspecific strains may be considered an expression of their relative susceptibility to infection. It will be noted in this series, as in my former studies, that lesions in the joints, the muscles, the stomach and duodenum, and the endocardium rank highest, which corresponds in general to the frequent occurrence of spontaneous infections in these structures in man and animals.

The occurrence of lesions in the gallbladder and in the pancreas of animals following injection of bacteria from the case of suspected cholecystitis without stone and with pancreatitis, and the relatively high incidence (21 per cent) of lesions in the gallbladder following injection of the ulcer strains, and in the stomach and duodenum (29 per cent) following injection of the gallbladder strains, suggests that the common association of two or more of these conditions in man may also be due to embolic infection by bacteria having affinity for the structures involved.

The demonstration that the foci of infection in tonsils and teeth, so commonly noted in patients with ulcer of the stomach, cholecystitis, pancreatitis, or appendicitis, contain bacteria which reproduce these respective diseases in animals, suggests strongly that such foci must be important factors in the production of these conditions in man. A focus of infection that is teeming with microorganisms, wherever found (it may be in the intestinal tract, which for mechanical reasons can neither heal nor drain), should be regarded as a test tube with permeable walls embedded in the tissues. In consequence the continued growth of the living bacteria and their products ultimately tends to overwhelm the protective mechanism of the host.

The careful elimination of foci of infection should become a routine procedure in both the medical and surgical management of these diseases. The focus should be removed before the mechanical factors, such as much scar tissue in chronic ulcer, gallstones in cholecystitis,

and fecal concretions or kinks from adhesions in appendicitis, have come to play a dominant part. The benefits should be especially noticeable in preventing acute attacks, in diminishing the number and severity of exacerbations in the chronic conditions, and in reducing the incidence of gastrojejunal ulcer after gastro-enterostomy, as emphasized by Eusterman and by Judd. The elimination of visible foci, however, will not prevent all these infections. The invasive power of the bacteria may be so great in some instances that forced entrance, as occurs in a focus, is not essential, and entrance may be gained through the un-abraded mucous membrane as in acute infectious diseases.

In the light of these experiments the place of localization after entrance into the blood stream depends largely on the peculiar infecting powers of the bacteria themselves. The fact that the peculiar infecting powers of the streptococci are lost on artificial cultivation, as well as on animal passage, would indicate that the strains isolated in these diseases are not specific, but modifications of the same strain. The reasons for the common presence in these diseases of organisms with respective elective localizing powers, again demonstrated in this study, are still obscure.

The elective localizing power of the colon bacillus has been demonstrated in cholecystitis and appendicitis, but only rarely. The results of the cultures of the tissues removed at operation and of the animal experiments indicate strongly that the colon bacillus is usually a secondary although important invader, especially in acute cholecystitis and appendicitis, and that it plays only a minor part in the etiology of ulcer of the stomach.

The results of my former studies have been corroborated and extended.^{2, 3, 6, 7, 8, 12, 14} The production by Mann of a specific cholecystitis by the intravenous injection of Dakin's solution supports the idea of elective localization from the chemical standpoint. The criticism of the size of the dose injected in my previous work has been met; the small number of bacteria from foci injected directly has been followed by elective localization. Streptococci have been found most constantly in the infected tissues and foci of infection in each of these diseases. They were usually the only organisms that had elective localizing power. With them the diseases, including ulcer, have been reproduced in animals. They have been repeatedly isolated from experimental lesions and the diseases again reproduced. The requirements for causal relationship of parasite and disease appear to be

fulfilled. The conclusion that streptococci are the chief cause of ulcer of the stomach, cholecystitis, and appendicitis, and, probably, pancreatitis, seems to be justified.

I wish here to express my appreciation to members of the staff of the Mayo Clinic through whom this work was made possible.

TABLE 1
ELECTIVE LOCALIZATION OF STREPTOCOCCI IN ULCER OF THE STOMACH, CHOLECYSTITIS,
AND APPENDICITIS

Source of streptococci.	Strains.	Animals.	Percentage of animals showing lesions in															
			Eyes.	Teeth.	Skin.	Muscles.	Joints.	Intestines.	Appendix.	Stomach and duodenum.	Gallbladder.	Kidneys.	Lungs.	Pericardium.	Myocardium.	Endocardium.	Nerves.	Central nervous system.
Ulcer of stomach	37	168	0	4	0	4	12	4	1	68	21	3	0	2	3	10	0	?
Cholecystitis . . .	12	41	0	0	2	7	17	17	0	29	80	5	5	0	2	10	0	?
Appendicitis . .	17	71	0	0	0	12	29	9	70	11	1	0	0	0	9	21	0	?
Myositis	24	159	0	7	3	75	31	0	0	15	2	11	7	6	14	11	11	?
Acute poliomyelitis	22	123	0	2	0	16	15	5	2	13	2	2	11	5	7	7	4	46
Miscellaneous . . .	71	212	4	3	4	12	9	4	1	9	1	9	7	0	4	12	4	?

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DUODENECTOMY: AN EXPERIMENTAL STUDY*

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A preliminary report has been made of the results of our experiments dealing with the removal of the duodenum. We are now submitting a further report of these experiments. The important physiologic and anatomic position of the duodenum and the desirability of determining whether it has a specific function or whether its physiologic action is merged with the rest of the gastro-intestinal tract were discussed in the preliminary report. It should be emphasized that our research deals also with the possible function of Brunner's glands.

REVIEW OF PREVIOUS WORK

A large number of experiments have been performed on the duodenum. The most important of these, and in fact the only ones presenting definite data, were published after our investigation had been started. The first experiments on the removal of the duodenum were performed in an attempt to determine the relative part the duodenum and pancreas might have in the production of experimental diabetes. The most important of these researches are those of Benzi and Reale, Pflüger, Ehrmann, Lauwens, Minkowski, Cimoroni, Tiberti, Rosenberg, and Bickel.

Benzi and Reale partially removed the duodenum in dogs, that is, they resected the portion not attached to the pancreas. By this method neither the common bile duct nor the pancreatic ducts were in any way molested and, on the other hand, none of Brunner's glands was removed.

Pflüger removed the duodenum and small intestine from frogs and dogs. In the latter species he performed the same operation that Benzi and Reale performed, that is, only a partial resection of the duodenum.

Ehrmann removed the duodenum from several dogs. The jejunum was anastomosed to the stomach. The pancreatic ducts were either

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ligated or implanted with the common bile duct into the stomach. The animals survived from a few days to a week, death evidently being due to or associated with trauma to the pancreas because wide-spread fat necrosis was always present.

Lauwens operated on several dogs. In five he made a gastro-enterostomy, transplanted the common bile duct with the minor pancreatic duct and a small amount of duodenal mucosa into the stomach, ligated the major pancreatic duct, and removed the duodenum. Four of the dogs died the first day after operation, and one lived until the thirteenth day. The other two animals were operated on in a similar manner except that the common bile and minor pancreatic ducts were transplanted to the skin. One of these animals died on the ninth day, and one was still alive on the thirteenth day.

Minkowski successfully removed the duodenum from two dogs. This seems to be the first successful duodenectomy. The continuity of the gastro-intestinal canal was established by a gastro-enterostomy. Bile flow was maintained by a cholecystenterostomy. The animals seem to have remained well, but since the investigator was interested in diabetes, the pancreas was removed in each animal and further data with regard to the duodenum were not given.

Cimoroni removed the duodenum from dogs in a one-stage operation. The pylorus, duodenum, and the first portion of the jejunum were removed. The jejunum was anastomosed to the stomach either by the regular posterior gastro-enterostomy technic, or by a Murphy button. The pancreatic ducts were tied and the common bile duct transplanted to the skin. Most of the dogs died immediately after operation. Four of them lived eleven, seven, six, and six days, respectively.

Tiberti removed the duodenum from nine dogs. He varied the type of operation. In three dogs he removed the duodenum, made a gastro-enterostomy, and transplanted the bile duct to the skin; in two entero-anastomosis was made; in two entero-anastomosis and cholecystenterostomy, and in two the operation was complicated by the removal of a portion of the pancreas. None of the animals lived very long after the operation, the longest period being five days.

Rosenberg removed the duodenum, although not completely, from five dogs. He performed gastro-enterostomy and cholecystenterostomy, and ligated the pancreatic ducts. Four of the animals died shortly after the operation; one was still alive on the twenty-third day.

Bickel removed the duodenum from two dogs. He performed gastro-enterostomy and transplanted the common bile duct and pancreatic duct to the skin. One of the animals lived ten days and the other four and a half weeks.

Gaultier studied the effect of injury by caustics to the duodenal mucosa in animals, and Zak reported two observations on the effect of caustics on the duodenum in man. Herlitzka observed the effect of the injection of vaselin and nicotin into the duodenum of frogs.

Maury, in an extensive research on high obstruction, concluded that the duodenal epithelium contained something of great importance to life, and particularly with regard to the toxic condition of obstruction. Matthews, on the basis of Maury's conclusions, performed several series of experiments in which the duodenum and jejunum were isolated and drained by various combinations of methods. From the results of these experiments he concludes that the removal of the duodenum is incompatible with life longer than seventy-two hours.

Stasoff studied the effect of removal of various portions of the gastro-intestinal tract. None of the animals in which he removed the entire duodenum survived. He was able to keep one animal alive in which the portion of the duodenum distal to the entrance of the common bile duct was resected.

Dragstedt, Dragstedt, McClintock, and Chase studied the effect of duodenectomy in two series of dogs. In eleven dogs the operation was performed in two stages. At the first operation the pylorus was divided, both ends closed, and an anterior gastro-enterostomy made with the middle jejunum. After the animals recovered from the first operation, a second was performed and the duodenum removed as far as the gastro-enterostomy. The bile and pancreatic ducts were tied and the gallbladder drained, in some cases into the jejunum, in others externally. Most of these dogs died within two or three days after the last operation; one lived twelve days. At necropsy a wide-spread, intra-abdominal fat necrosis was usually found. In one series of five dogs the common bile duct was ligated and sectioned, the pylorus divided, the pancreas opposite the pylorus ligated and divided with a cautery, and the entire duodenum with the adherent pancreas as well as the upper jejunum removed. The middle jejunum was sutured to the divided pylorus, and the gallbladder drained. Most of these animals died on the fifth or sixth day, but one lived three weeks and one three months.

The dog that survived three months, however, showed very marked nutritional disturbances and was kept alive for that period only by careful feeding and special attention.

Grey removed the duodenum in three stages, allowing an interval of several weeks between each stage. The first stage consisted of dividing the common bile duct between ligatures and anastomosing the gallbladder to the proximal jejunum. After the animal had recovered, the second stage was performed. This consisted of isolating the major pancreatic duct and transplanting it into the jejunum a short distance from the site of the cholecystenterostomy opening. At the same time the minor pancreatic duct was ligated and sectioned. At the third stage the duodenum was removed.

Many animals succumbed at various stages of the operation, but one survived all three operations and lived in a normal condition for nine and one-half months after the total removal of the duodenum; it then died suddenly, apparently from intestinal obstruction following adhesions.

Moorhead and Landes also removed the duodenum of the dog in three stages. In the first stage the pylorus was sectioned, the duodenal end invaginated and closed, and the proximal jejunum anastomosed to the gastric end. Two weeks later the common bile duct and major pancreatic duct were transplanted into the jejunum just distal to the gastrojejunal anastomosis. After another interval of two weeks the duodenum was removed. Only the mucosa was removed from the pancreatic portion of the duodenum. Dogs operated on in this manner lived in a normal state of health.

A few general statements are justified from this brief review of the data of previous workers on the effects of duodenectomy. As I have stated, the first investigators were interested in the problem only as it might effect the problem of experimental diabetes. Only a very small percentage of their animals lived after operation. In most of the few that survived the duodenum was not removed completely, and in the very few instances in which it seemed reasonably certain that the complete extirpation would be successful, the duodenal phase of the experiment was sacrificed for the pancreatic phase.

It does not seem that experiments dealing with the short circuiting of any particular portion of the gastro-intestinal tract parallel those in which the same portion has been removed surgically. Many of the short circuiting operations produce toxic conditions. For that reason

the experiments of Matthews should be classified with those on intestinal obstruction and not on duodenectomy.

The last three investigators proved that a dog could live, at least for a relatively short time, after duodenectomy. Dragstedt and his collaborators clearly showed that the dog can survive duodenectomy, but their work is open to the same objections as that of many of the earlier workers, that the duodenectomy was complicated by a loss of pancreatic function, and in some instances, of function of the bile. The results of Grey, one of whose animals lived the longest after duodenectomy, and the results of Moorhead and Landes prove that duodenectomy is compatible with life and perfect health in the dog for relatively short periods.

TECHNIC OF REMOVING THE DUODENUM

In our first experiments we attempted to follow the technic employed by previous workers in which two-stage or three-stage operations were performed. This attempt proved as fruitless in our hands as in the hands of others; it seemed as if only a small percentage of animals would live after the second or third operation. We then devised a one-stage operation, after the plan of the two-stage operation. Most of the operations performed by this method were partial or complete failures, the animals dying because of the long operation or from intercurrent disease. One animal lived seventeen days and died from intussusception of the small intestine. One in which the pancreatic ducts were ligated lived forty-one days (Protocol 1).

Because of the unfavorable results a one-stage operation consisting of four steps was developed: (1) dissection of the duodenojejunal fold, mesoduodenum, lesser omentum, and ligation of the blood vessels supplying the upper jejunum and duodenum; (2) separation of the pancreas from the duodenum and isolation of the major pancreatic duct and the common bile duct together with the lesser pancreatic duct; (3) removal of the entire duodenum in connection with a portion of the proximal jejunum and distal pyloric portion of the stomach; and (4) implantation of the bile duct together with the minor and the major pancreatic ducts into the jejunum. By this method the duodenectomy can be performed quickly, and the other organs involved, such as the bile duct, both pancreatic ducts, the pancreas, and the alimentary tract, can be restored, as nearly as possible, to the normal state (Figs. 57 and 58).

The animal was fasted for twenty-four hours. Ether anesthesia was employed and all operations were performed with aseptic technic. The duodenum was exposed through a right rectus or midline incision (Fig. 52). The duodenojejunal junction was found and the duodenojejunal fold cut. The branches of the mesenteric vessels, usually three or four, which run to the distal duodenum and proximal jejunum, were doubly ligated and sectioned. This procedure mobilized the proximal portion of the jejunum. The mesoduodenum was cut to the point where the pancreas becomes adherent to the duodenum. In order that the



FIG. 52.—The anatomic relationship of the duodenum in the dog. The portion to be resected is included between the dotted lines.

subsequent gastrojejunal anastomosis might be performed with ease, the lesser omentum was partially divided; usually it was also necessary to ligate and section several blood vessels.

The common bile ducts and the pancreatic ducts were located and exposed. The bile duct and minor pancreatic duct, together or close to each other, open into the duodenum from 5 to 8 cm. from the pylorus, and the major pancreatic duct opens from 2.5 to 5 cm. distally. After exposure of the ducts the duodenum was carefully but boldly dissected from the pancreas, beginning at the caudal end. The branches

of the pancreatic-duodenal vessels which enter the duodenum from the pancreas were tied with fine silk or catgut ligatures and divided close to the former. The bile duct passes behind the duodenum, perforates the muscular coat of the latter, and, after running for 1 cm. or more in the submucosa, opens into the bowel, closely associated with

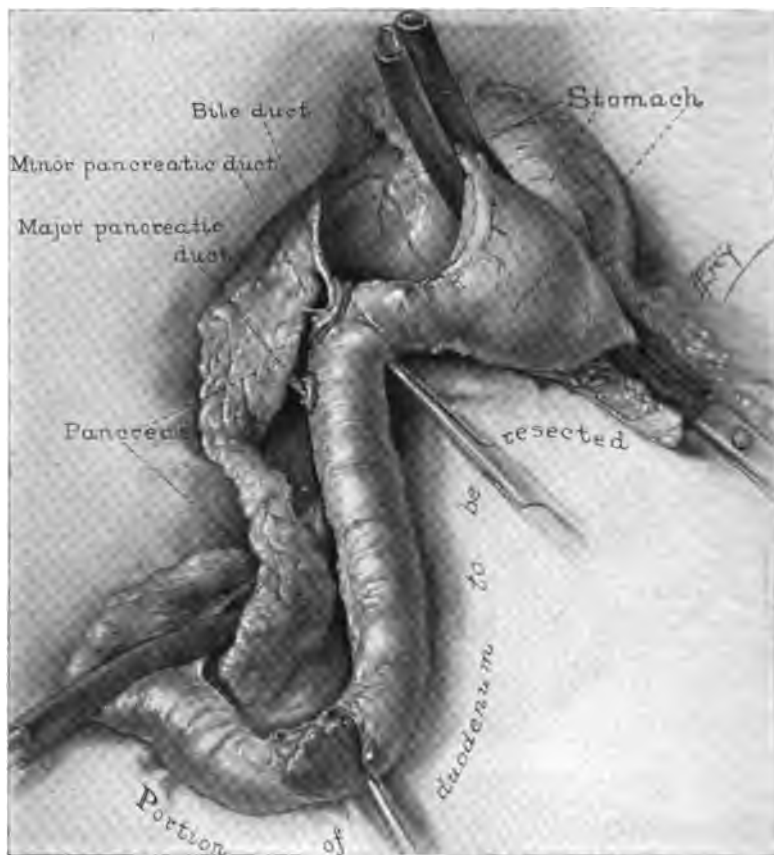


FIG. 53.—The duodenum of the dog before resection and after complete separation from its ligaments, blood vessels, and pancreas. The ducts are completely isolated and ready to be sectioned just as they pass through the mucosa of the duodenum.

the minor pancreatic duct. An aneurism needle was placed under the exposed portion of the duct, placing it on a tension. The muscular coat of the duodenum along both sides of the entire course of the duct was incised longitudinally with a small sharp pointed scalpel and the duct perfectly isolated up to its orifice. The same procedure was repeated

on each of the pancreatic ducts. At this point of the operation the duodenum was free with the exception of its attachment to the stomach and jejunum and to the bile and pancreatic ducts (Fig. 53). Various methods were tried of treating the orifices of the ducts. By far the easiest method consisted of excising and leaving a small ring of duodenal mucosa around the duct. Owing to the disturbance of the circulation this little piece of mucosa always appeared dark red, and it seemed reasonable to suppose that it would not live. However, since such a method involves a careful histologic examination of the orifice of the ducts at necropsy in order definitely to determine that no duodenal mucosa is present, it seemed best to devise a technic which would be free from such suspicion. In a few operations we followed the method of previous operators and thoroughly scraped off the mucosa. The serious objection to this method is that scraping the mucosa is liable to cause contamination. The method which was found most satisfactory and which obviated the possibility of contamination and the danger of leaving duodenal mucosa is as follows:

The muscularis of the duodenal wall is cut about 1 cm. from the opening of the duct in the bowel and pushed back, making a cuff around the duct which extends toward the lumen of the duodenum. The duct is then sectioned just at its point of entrance into the bowel. In this manner the lumen of the duodenum is not entered and duodenal mucosa is not attached to the ducts. The minor pancreatic duct can usually be freed with the bile duct. Rarely is it necessary to cut the former because of an anomaly in position. It is very important that during the manipulation the pancreas is kept warm and well protected from contamination and drying. All unnecessary trauma must be avoided. The vessels supplying the duodenal wall must be ligated and divided close to the duodenal wall. Many of the failures recorded by other investigators and a few of our own have been due to trauma of the pancreas.

The next step in the operation is the removal of the entire duodenum. Rubber covered clamps are placed on the stomach and the jejunum. The entire segment of bowel from which the blood supply has been ligated is removed. This includes a segment of the pyloric region of the stomach (1 or 2 cm. proximal to the pyloric ring), the entire duodenum, and from 10 to 15 cm. of the proximal jejunum. The continuity of the intestinal canal is restored by direct anastomosis of the opened end of the stomach to the sectioned jejunum. Thus a

segment of the jejunum occupies the exact site which had been occupied by the duodenum (Fig. 54).

The final step in the operation is to transplant the ducts. Two guides of No. 00 plain catgut threaded on straight cambric needles are attached on opposite sides of each duct (the minor pancreatic duct is included with the bile duct). A site on the wall of the portion of the



FIG. 54.—The duodenum resected and the jejunum anastomosed to the pyloric end of the stomach. The next step in the operation is the transplantation of the ducts. Note the cuff of muscle around each duct.

jejunum which occupies the position of the duodenum is selected to prevent tension on the ducts. At this site, which is at about one-third the circumference of the jejunum from the mesenteric attachment, a purse-string suture of No. 00 catgut is placed. The purse-string forms a circle of about 8 mm. in diameter. With a sharp pointed knife the center of the circle is pierced and the opening enlarged by stretching

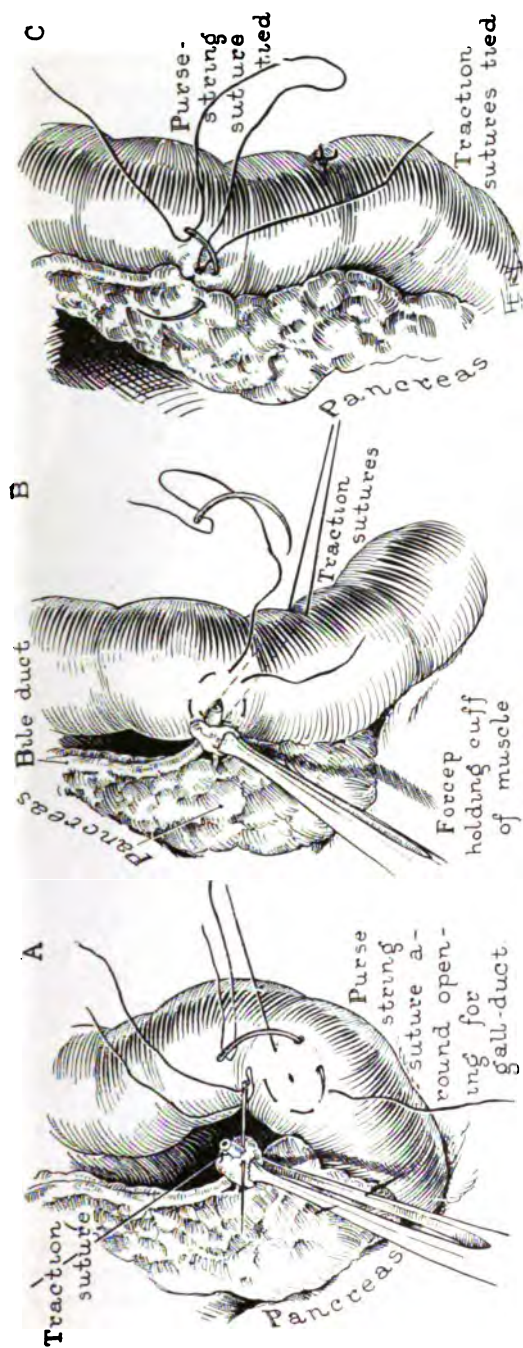


FIG. 55.—Steps in the transplantation of the ducts. A, Traction and purse-string sutures in position. B, The duct being pulled into the jejunum. C, The transplantation completed.

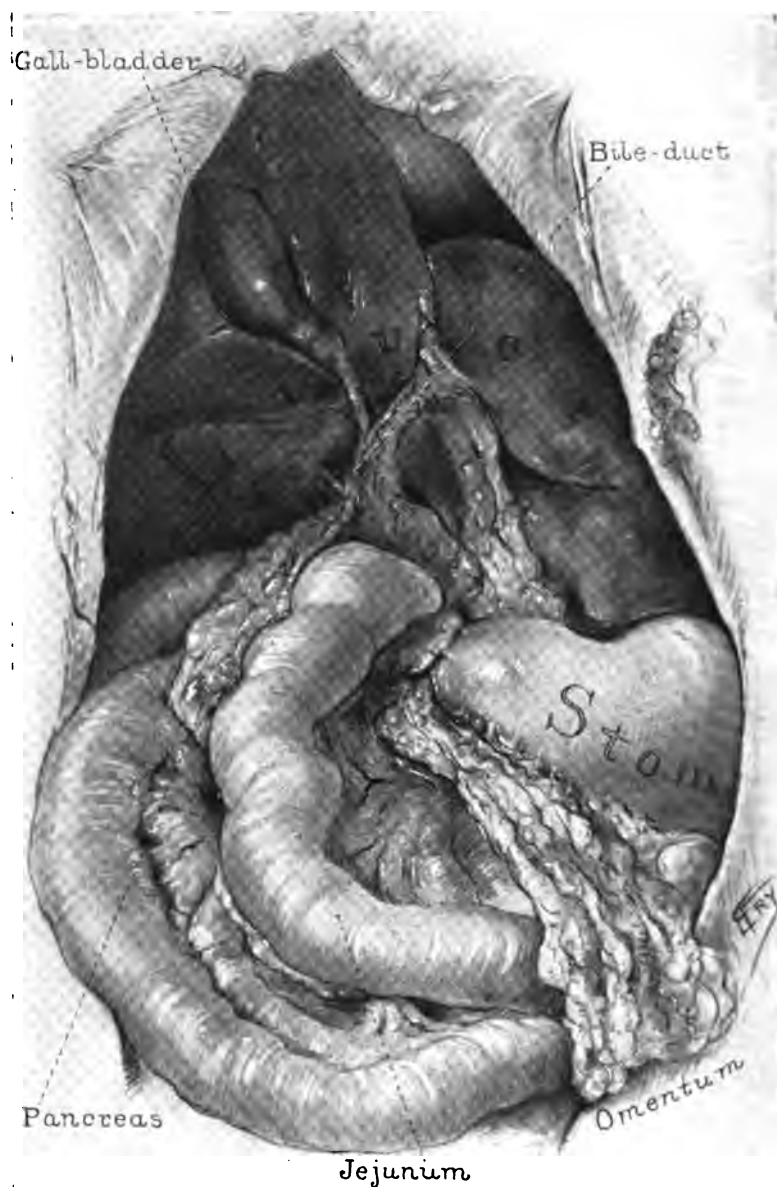


FIG. 56.—The operation completed in the dog. The jejunum occupies the position previously occupied by the duodenum. An almost complete reconstruction of the gastrointestinal tract has been accomplished. The sites of transplantation of the ducts are marked by the indentation of the contour of the jejunum.

with sharp pointed forceps to equal the diameter of the duct. Through this opening the needles of the guides are passed and pierce the opposite side of the bowel about 2 cm. below their entrance and about 0.5 cm. apart. The duct is drawn into the lumen of the jejunum and the guides tied. The purse-string suture is tied and, if necessary, a few additional sutures are taken and a tag of omentum sutured around the duct (Fig. 55). When this is finished the bowel is slightly constricted, but it is always patent for the passage of gas and liquids (Fig. 56). The constriction disappears when the fine catgut is absorbed. The muscularis which is left around the duct serves to plug the opening through which it has been drawn.

There are many possibilities for technical errors. In our experiments the failures have been due to (1) too small an opening of the anastomosis of the jejunum to the stomach, (2) suturing the common bile duct too firmly in the intestinal wall, producing partial obstruction, and (3) trauma to the pancreas (this error only occurred in cats). It is interesting to note that we rarely had a failure of the transplantation of the pancreatic duct in this series of experiments.

RESULTS OF REMOVAL OF THE DUODENUM IN VARIOUS SPECIES OF ANIMALS

With slight modifications in the technic described, necessary because of anatomic variations in the different species of animals, the duodenum was removed from five species, dog, cat, hog, goat, and monkey. The best results were obtained in the dog, cat, and hog, and conclusions are based on the data obtained from the experiments on these three species.

The dog.—Most of the experiments were performed on the dog and, since the technic was devised mainly for the dog, it was carried out exactly as described. Our observations included (1) the general condition of the animal, (2) the movements of the gastro-intestinal tract, and (3) the secretory activity of the stomach. We had also planned to study the secretion of the pancreas and liver, but as a few preliminary observations made it quite evident that the loss of the duodenum would not produce so great a change, if any, in the secretory activity of these glands, as the transplantation of their ducts, we did not make any extensive observations.*

*Our observations on the secretory activity of the stomach are not completed.

We have not been able to show that the removal of the duodenum in the dog, unaccompanied by sequelæ of errors of the technic of the operation, in any way affects the life or general health of the animal except in relation to the possibility of ulcer. All the animals in which the operation was technically perfect remained in seemingly normal

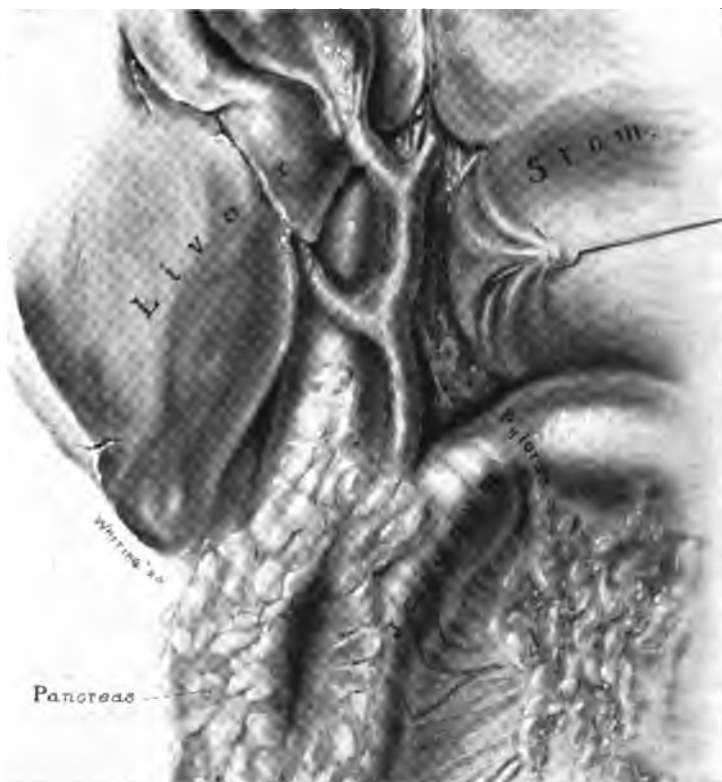


FIG. 57 (Dog D 37).—The site of operation at necropsy 490 days after duodenectomy. Grossly the pancreas and liver appear to be normal. The extrahepatic biliary tract is slightly dilated and the walls thickened. The gastrojejunal anastomosis is hardly discernible. (Operation by Kawamura.)

condition. The appetite was always good; the weight did not vary any more than in laboratory dogs not operated on; nothing was noted which could be attributed to the loss of the duodenum (Protocol 2).

A few of the duodenectomized dogs showed a steady loss of weight and strength after operation. At necropsy in these animals an error of technic in one or two points was noted. In some of the animals a

dilated common bile duct and marked infection of the entire biliary tract were found. Evidently the transplantation of the ducts did not restore a sufficiently normal condition to prevent infection. In the others the anastomosis of the jejunum to the stomach was not of sufficient caliber to allow the stomach to empty correctly; consequently there were considerable gastric retention and dilatation.

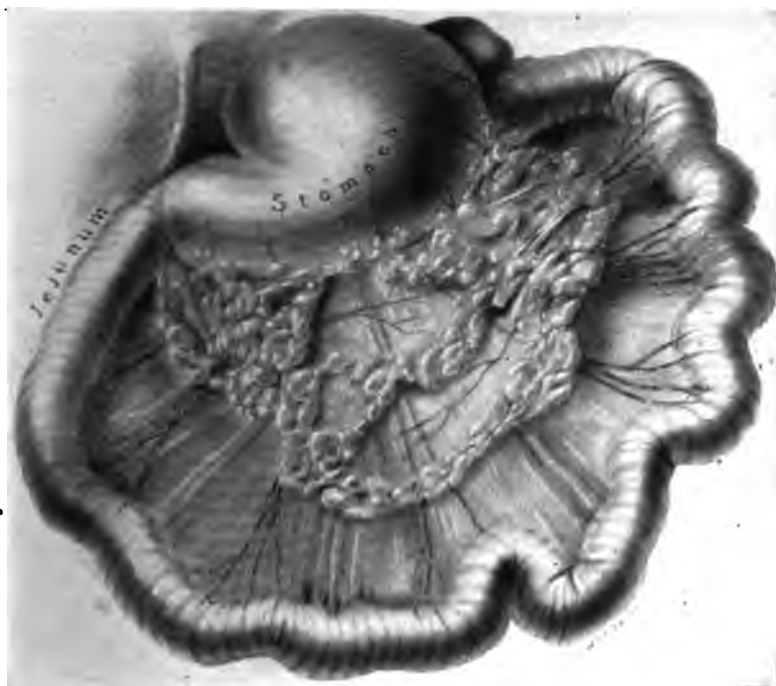


FIG. 58 (Dog D 37).—The stomach and jejunum 490 days after duodenectomy. The chief evidence of the absence of the duodenum is that the loop of intestine proximal to the stomach has a free mesentery, that is, the ligament of Treitz is absent. (Operation by Kawamura.)

The blood of some of the dogs was examined with regard to cell count, hemoglobin, carbon dioxide combining power, and hydrogen ion concentration, before and after duodenectomy. No differences were noted which appeared to be owing to the duodenectomy.

In several of the animals the gastro-intestinal tract and the passage of a standard barium meal were examined by means of the roentgen ray. The method consisted of making observations and plates on the course of the standard barium meal two or three times before duode-

nectomy and at various times after. The barium meal consisted of equal parts of barium sulfate, saturated gum acacia solution, and condensed milk. Fifteen cubic centimeters for each kilogram of body weight of the solution was administered by stomach tube. Observations were made immediately after the administration of the meal and at definite subsequent periods until the meal had passed through the animal.

In general, noteworthy differences were not noted in the passage of the standard barium meal before and after duodenectomy. In most animals the meal started to leave the stomach sooner after duodenectomy than before. This was attributed to the loss of the pyloric sphincter. In a few of the animals the stomach emptied slightly faster after operation than before and in a few others the emptying was delayed. In all cases the changes were slight and did not seem to differ from the slight changes noted by repeated observations on normal dogs. Of course it is possible that if various types of meals had been administered, differences might have been noted. The picture of the gastro-intestinal tract always appeared to be normal. A few preliminary observations in the secretory activity of the stomach after duodenectomy were made. No noteworthy change was found.

The cat.—The duodenum is easily removed from the cat, but the operative results are not good. The technic was the same as that used in dogs. Most of the cats recovered from the immediate effects of the operation, but did not do well and died within a few days. At necropsy the cause of death usually seemed to be trauma to the pancreas; in no instance could death be attributed to loss of the duodenum. One of the cats recovered and appeared normal for 168 days, when it died from an intercurrent disease. From this one complete experiment we can definitely state that duodenectomy is compatible with life and health in the cat (Protocol 3).

The hog.—The hog was selected as an omnivorous type of animal. Duodenectomy is difficult in this species. The bile and pancreatic ducts empty separately. For expedience and in order to remove all of the duodenum, it was found best to section the intestine at the duodenojejunal juncture, invert the end of the jejunum, and unite the jejunum slightly more distally to the end of the stomach. The operation was performed on only one hog, and the success and results of the experiment did not seem to warrant further investigation in this species. The animal recovered from the operation, developed, and fattened normally (Protocol 4).

DISCUSSION

This brief review of our experiments readily shows that the duodenum is not necessary for life, and the fact that noteworthy changes were not observed make it appear that its function does not differ greatly from that of the rest of the intestinal tract.

Only one positive finding was obtained in the entire series of experiments. In two of the dogs a large ulcer was found on the jejunal side of the suture line of the gastrojejunal anastomosis. In one of the animals the ulcer perforated, causing peritonitis and death (Dog C 991,



FIG. 59 (Dog C 991).—A perforating ulcer on the jejunal side of the suture line which produced peritonitis and death 515 days after duodenectomy.

Table 1 and Fig. 59) 515 days after duodenectomy. The other animal came to necropsy 383 days after duodenectomy and a large ulcer with a hard base was found (Dog C 919, Table 1 and Fig. 60).

Eleven duodenectomized dogs were kept under observation for from ten to thirty months. One of these is still alive. Of the ten coming to necropsy, two had ulcers. Since peptic ulcer of the subacute or chronic type is very rare in the dog, this seems significant.¹¹

At the suggestion of Dr. C. H. Mayo we are making a more comprehensive study of the effect of duodenectomy in relation to gastric secretion, and are also studying the possible function of Brunner's



FIG. 60 (Dog C 919).—A deep ulcer on the jejunal side of the suture line, noted at necropsy, 393 days after duodenectomy. The ulcer had penetrated to the muscularis and had a hard base. The opening of the common bile duct is at a, the opening of the pancreatic duct at b.

glands. From these studies we hope to determine the reason for the presence of these ulcers.

SUMMARY

The investigation was undertaken for the purpose of determining the effect of removing the duodenum. A one-stage operation for removal of the duodenum was developed. The duodenum was removed from

the dog, cat, hog, goat, and monkey, although long-continued observations were made only on the dog, cat, and hog. Careful studies on these three species did not reveal any noticeable changes following the duodenectomy. In the dog observations were carried on more than two and one-half years after operation. The animals remained in good condition. No data have been secured to show that the duodenum is of great importance in any of the species studied. However, in two of the ten dogs studied a typical peptic ulcer occurred on the jejunal side of the gastrojejunal anastomosis. Whether this bears any relation to the loss of the duodenum or any specific part of it, as Brunner's glands, is to be determined.

PROTOCOL 1

August 7, 1918, Experiment 552, Dog C 673, an adult female bull terrier, in good condition, weighing 14.8 kg. Under ether anesthesia a two-stage operation in one stage was attempted. The pancreatic ducts were traumatized, which necessitated ligation. The duodenum was removed and an end-to-end anastomosis between the jejunum and the stomach made, and the bile drained by a cholecystenterostomy.

The animal recovered from the immediate effects of the operation and remained in fair condition for forty-one days and then died. The cause of death was not determined, but probably it was partially associated with the ligation of the pancreatic ducts.

PROTOCOL 2

December 11, 1918, Experiment 892, Dog C 878, a male mongrel shepherd, weighing 20.7 kg. The duodenum was removed at a single operation. The animal recovered from the operation and remained in excellent condition.

December 31, 1918, the animal was in good condition, its weight was 19 kg.; it remained in good condition. January 8, 1919, its weight was 17.9 kg., January 14, 19.9 kg., January 23, 19 kg., and February 18, 19.8 kg. July 3, the animal was fat, its weight was 21.2 kg., December 19, one year after operation, the animal was in good condition, its weight was 18.3 kg., January 6, 1920, 21.4 kg., March 4, 20 kg., June 4, 20.2 kg., July 30, 19.3 kg. The animal remained in good condition for several months longer and then lost slightly in weight. December 12, 1920, it weighed 16.4 kg., but it soon recovered normal weight. June 30, 1921, two and one-half years after duodenectomy, it was in excellent condition and weighed 20 kg. (Fig. 61).

PROTOCOL 3

November 1, 1919, Experiment 747, Cat 173, a male adult in good condition, weighing 2416 gm. A very fine silk was used for all sutures except for the purse-string suture in transplanting the ducts. Only the pancreatic duct, which empties with the common bile duct, and the common bile duct were transplanted. The animal recovered from the operation and remained in excellent condition for many weeks.

In March, 1920, it developed distemper. Following this it lost some weight, but remained in fair condition, although it coughed considerably and had a chronic nasal discharge. Pneumonia developed, and the animal died May 7.

Necropsy was performed shortly after death. Both lungs were markedly involved by the pneumonic process. The site of operation was in good condition. The common

bile duct was slightly dilated. Grossly the pancreas was normal. Effect of the operation could not be discerned either grossly or microscopically.

PROTOCOL 4

June 10, 1919, Experiment 359, Hog 1, a Duroc-Jersey male, approximately six months old. The animal was decidedly a runt, weighing only 23.4 kg.; otherwise it was in excellent condition. The technic used in the dog was attempted. The operation was very difficult. The mesentery was too short to allow the direct anastomosis of the end of the jejunum to the pylorus, so that the jejunum was sectioned at its point of origin and the end united to the pylorus by an end-to-end anastomosis. The transplantation of the common bile duct and the pancreatic duct, which are separate in the hog, was accomplished with considerable difficulty.



FIG. 61 (Dog C 878).—Duodenectomy two years and six months before. The animal appears the same as before operation.

The animal was quite sick for the first few days, but soon recovered from the immediate effects of the operation. Bile appeared in the urine and the scleras had a slight yellow tinge. The stools showed evidence of lack of bile. After the first week the animal's appetite became normal, bile disappeared from the urine, and the stools gradually returned to normal.

May 24, 1919, the animal was practically normal; it weighed 25 kg.

June 20, the animal was in good condition; it weighed 27.5 kg. It was then sent to the farm where it grew and developed normally. It was kept under daily observation, but no detailed data were recorded. It was fed moderately, but never given a full fattening meal.



FIG. 62 (Hog 1).—Thirty days after duodenectomy; animal weighs 27.5 kg. Compare with Figure 63.



FIG. 63 (Hog 1).—Three hundred two days after duodenectomy; animal weighs 130 kg. Compare with Figure 62.

November 6, 1919, the animal weighed 95.5 kg.

February 26, 1920, the animal weighed 130 kg.

February 27, 1920, the animal was killed, and necropsy performed immediately. The animal was in good condition, moderately fat, but not nearly so fat as it could have been if a heavier feed had been given. The incision was marked by a faint scar. On opening the abdomen a few rather dense adhesions were found at the site of operation; otherwise it was in excellent condition. The biliary tract, however, seemed to be infected and a few small stones ranging from 2 to 4 mm. in diameter were found scattered throughout the liver. The pancreatic duct transplantation had been a partial failure because a portion of the pancreas was infiltrated with fat, although there were large areas of pancreatic tissue interspersed throughout the fat. Grossly and microscopically all other organs were normal. Microscopically the liver showed few pathologic changes and the remaining pancreatic tissue was normal (Figs. 62 and 63).

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TABLE 1
POSTOPERATIVE COURSE OF TEN DUODENECTOMIZED DOGS

Animal.	Length of life after duodenectomy.	Cause of death.
	Days.	
Dog C 750	325	Etherization.
Dog C 729	327	Obstruction resulting from adhesions around an infected silk suture at the site of the intestinal anastomosis.
Dog C 802	372	Volvulus of large intestine.
Dog C 991	515	Peritonitis following perforation of ulcer at site of intestinal anastomosis.
Dog D 37	490	Etherization.
Dog D 38	556	Results of another experiment.
Dog D 39	555	Results of another experiment.
Dog C 919	393	Results of another experiment.
Dog D 86	480	Etherization.
Dog D 339	355	Etherization.

JEJUNAL ULCERS*

E. STARR JUDD

Gastrojejunostomy for ulcer of the stomach or of the duodenum offers the patient a good prospect of complete and permanent relief of all symptoms. Because of the frequency of malignancy of the stomach and because a greater proportion of gastric ulcers is cured if the ulcers are excised in addition to gastro-enterostomy, excision should always be performed. In duodenal ulcers, either gastro-enterostomy or excision is sufficient.

Unsatisfactory results are most often due to a gastrojejunostomy in cases in which no ulcer exists. The basis for the operation in these cases is the clinical history and either no attempt is made to demonstrate the ulcer or it is assumed that an ulcer is present when none can be located. As a matter of fact an ulcer of the stomach or of the duodenum is seldom present without being demonstrable. More often the cause of the symptoms is located elsewhere, which is further justification of a very good rule not to operate unless an ulcer can be demonstrated beyond a question of doubt. The fundamental basis for surgical procedures must be pathologic and not clinical. The so-called vicious circle is now seldom heard of, although a few years ago it was a much dreaded complication in these cases. The disappearance of this syndrome has been brought about partly by improvement in technic, but more particularly by the recognition of the importance of avoiding operation when no ulcer exists.

The particular phase of ulcers that I wish to discuss is the formation of secondary ulcers some time after the operation. Jejunal ulcer is one of the most serious and perhaps one of the most common after-complications of gastro-enterostomy. It occurs either in the line of anastomosis as a so-called gastrojejunal ulcer, or in the jejunum below the line of anastomosis as a true jejunal ulcer. The lesion is usually single, although multiple ulcers at the site of the anastomosis are not

* Presented before the Association of Surgeons of St. Louis, January, 1921. Reprinted from *Surgery, Gynecology and Obstetrics*, 1921, xxxiii, 120-126.



FIG. 64 (Case A66081).—Jejunal ulcer showing gastrocolic fistula at *p*.

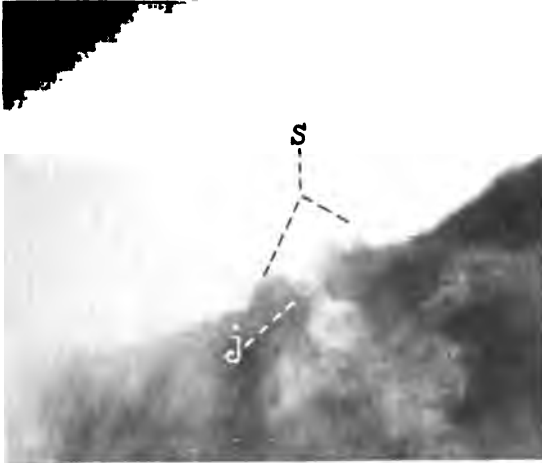


FIG. 65 (Case A98054).—Jejunal ulcer. *s*, Deformity of stoma; *j*, narrowing of first part of the jejunum.

uncommon. In such ulcers the lesion in the mucous membrane is usually very small and, I believe, is always entirely limited to the intestinal side. Edema and adhesion to the surrounding tissues is marked

and suggests that in most of these cases there has been a slow leak from a small perforation. The lesion of the mucous membrane, although it is entirely within the mucosa of the small intestine, is most often very close to the gastric mucosa. In all of the cases in the Clinic the lesion seemed to be distinctly jejunal. This differs from Paterson's report of cases, for he says that in most instances the ulcer is some little distance from the stoma. Often it is situated directly opposite the opening in the stomach and nearly always in the efferent loop; it may be fully 10 cm. from the anastomosis.

The frequency with which jejunal ulcers occur following gastro-enterostomy is difficult to estimate; Paterson reports that they occur in from 1 to 2 per cent of cases. In the Clinic we have found fifty-five definite secondary ulcers in 4,324 gastro-enterostomies, but in all probability the percentage is somewhat higher because in some instances the disturbance from the ulcer may not be sufficient to bring the patient back for treatment and, furthermore, with the return of symptoms he is likely to seek treatment elsewhere. Thus we may not see all of our patients who develop the condition. We have operated on forty-six patients for jejunal ulcer in whom the primary operation had been performed elsewhere.

ETIOLOGY

A satisfactory explanation of the cause of jejunal ulcer can best be found in the etiology of the original ulcer. In not a single case in our experience did an ulcer of the jejunum occur as a primary lesion, and we have found but one case mentioned in the literature, that reported by Schmilinsky in a patient sixty-three years of age who had a chronic ulcer of the jejunum which was resected. In the discussion of this report Frankel and Katz stated that they had seen a similar case, but that they had attributed the ulcers to syphilis. Schmilinsky concluded that his case might have been syphilitic in origin, although he had no proof of this. At any rate, if jejunal ulcer occurs at all as a primary lesion it is extremely rare. It is interesting to note that jejunal ulcer following operation almost always occurs only following gastro-enterostomy for ulcer. One case has been observed in the Mayo Clinic after resection of the stomach for cancer. There are no cases following plastic procedure around the pylorus.

Undoubtedly the principal cause of the secondary ulceration is the action of the acid gastric secretion on the mucous membrane of the

jejunum. In most cases of ulcer there is a hyperacidity or hypersecretion and unless this is neutralized by the bile and pancreatic secretions it may have a very toxic and destructive influence on the epithelium of the intestine. In all of Paterson's cases and in more than 60 per cent of the cases in the Clinic the acids were high even after gastro-enterostomy. In the ordinary case the acid chyme is neutralized as it enters the intestine by the action of the bile and pancreatic fluids. If, how-



FIG. 66 (Case A98939).—*s*, Deformity of stoma; *j*, narrowing of jejunum in a case of jejunal ulcer.

ever, there is any unusual change in either the amount or rate of secretion of the acid fluids of the stomach, or any change in amount, or rate, or character of the secretion of bile or pancreatic juice the neutralizing influence may be destroyed, and the contents of the jejunum may become strongly acid. Undoubtedly it is some such disturbance which allows the unneutralized acid chyme to reach the jejunum and to afford an opportunity for the formation of jejunal ulcer.

Permanent suture material has also been a factor in the production

of many ulcers, particularly those close to the gastrojejunostomy opening. In the Clinic large strands of silk and linen have been found hanging from the ulcerated area several years after the operation and undoubtedly this foreign material had kept up irritation and infection. In the series of 101 jejunal ulcers in the Mayo Clinic, herewith reported, nonabsorbable suture material was found in nine cases of the fifty-five in which the primary operation was performed in the Clinic, and in



FIG. 67 (Case A112391).—*s*, Deformity of stoma; *j*, narrowing of the jejunum near stoma in a case of jejunal ulcer.

seventeen of the forty-six in which the primary operation was performed elsewhere (Table 1). Recently Dr. Sistrunk cut off a gastro-enterostomy for a patient operated on twelve years before. Heavy black silk sutures were found, but no evidence of infection or ulceration; nevertheless, it seems reasonable to assume that since nonabsorbable material has been discarded fewer jejunal ulcers will develop.

Trauma to the tissues of the jejunum during the operation must be considered a factor in the formation of some ulcers. It has been con-

TABLE 1

JEJUNAL ULCERS FOLLOWING GASTRO-ENTEROSTOMY IN 101 CASES
(Mayo Clinic, January 1, 1912 to January 1, 1921)

	Cases.
Males.....	90
Females.....	11
Ulcers at the stoma.....	93
Ulcers below the stoma.....	8
No evidence of primary ulcer.....	15
Foreign material found at secondary operation.....	26
Foreign material found at secondary operation, but not in vicinity of the ulcer.....	3
Primary operation (Mayo Clinic).....	55
Foreign material found at secondary operation.....	9 (16.25 per cent)
Primary operation (elsewhere).....	46
Foreign material found at secondary operation.....	17 (37.77 per cent)
<i>Types of secondary operation</i>	
Excision and cutting off of gastro-enterostomy.....	28
Excision and reconstruction of gastro-enterostomy.....	16
Excision and cutting off of gastro-enterostomy:	
New gastro-enterostomy (one anterior).....	11
New gastro-duodenostomy (one anterior).....	12
Partial gastrectomy.....	8
Excision of ulcer and plastic operation.....	16
Excision of ulcer and pyloroplasty.....	10 101
<i>Findings at secondary operation</i>	
Large ulcers (10 perforated and 2 associated with hour-glass stomach).....	30 } 6 hard
Small ulcers (3 perforated).....	42 } 10 calloused
Small acute ulcers.....	4
Perforations (no mention of type of ulcer).....	11
Indurated ulcers.....	2
Type of ulcer not classified.....	12 101
Marked stricture of the jejunum.....	3
Dilated jejunum.....	2
Edema.....	3
Linitis plastica.....	1
Marked obstruction.....	8
Adhesions of variable degree.....	54
<i>Additional procedures at time of secondary operation</i>	
Appendectomy.....	10
Cholecystectomy (one with pyloroplasty).....	4
Knife excision of old duodenal ulcer.....	9
Cautery excision of old duodenal ulcer.....	1
Herniotomy.....	5
Adhesions broken up.....	13
Partial gastrectomy with anastomosis for polypoid carcinoma and duodenectomy for duodenal ulcer.....	1 43
Gastro-enterostomies for benign ulcer from January 1, 1912 to January 1, 1921.....	4324

tended that the use of rubber-guarded clamps on the stomach and jejunum is a cause, but ulcers have been reported when these were not used, and it has also been shown that often the jejunal ulcer forms in the part of the efferent loop below the clamps; in eight of the series of 101 jejunal ulcers the lesion was several centimeters from the anastomosis; in one case it was 10 cm.

Infection must play some part in the etiology of these lesions. The cut surfaces of the stomach and of the jejunum are exposed to the infection from the original ulcer during operation and during the healing process which lasts about fourteen days. It is questionable whether or not infection from the surface of the ulcer carried to the freshly cut area would result in the same type of lesion. Furthermore, in fifteen of



Fig. 68 (Case A127252).—*a*, Deformity of stoma; *j*, narrowing of the efferent loop of the jejunum in a case of jejunal ulcer.

the 101 cases there was no evidence of an original ulcer. Moynihan mentions two such cases. The gastro-enterostomy had been performed for other conditions, such as dilatation or prolapse, so that infection from the ulcer was not present at the time of the operation. This seems to show that a particular type of infection is not necessary for the formation of the secondary ulcer.

CLINICAL MANIFESTATIONS

The time of onset of symptoms of jejunal ulcer varies from almost immediately after the gastro-enterostomy to eight or ten years. In one of our cases there was relief for a very short time and then a return of all

the symptoms, and within five weeks after the original operation a definite secondary ulcer was demonstrated by the roentgen-ray examination. The second operation, performed at that time, revealed a jejunal ulcer much larger than the original duodenal ulcer. This case also illustrates what seems to be a tendency to ulcer-forming found in an occasional patient. After the second operation, which was excision of the jejunal ulcer and plastic reestablishment of the gastro-enterostomy, the patient was placed on definite ulcer management in which he had been trained for a year previous to the first operation. He remained free from symptoms for three months and then had a return of all of the signs and symptoms of a jejunal ulcer which was again demonstrated by the roentgen ray. At the third operation, just three months after the first, a jejunal ulcer was found on the afferent side of the stoma, which was opposite the location of the former jejunal ulcer. At this time the gastrojejunostomy was undone and the duodenal ulcer excised. The patient has now been free from symptoms for about two years. Several cases similar to this one have been reported, and even three or four operations for recurring ulcers have been performed. A detailed study of the blood of the patient was made and a thorough examination of the foci for any source of infection, but reason for his tendency to develop ulcers could not be found.

Usually all symptoms are completely relieved following gastro-enterostomy for from six months to one year (Eusterman); then there is a gradual return of all of the evidences of ulcer. Often the manifestations are not quite so severe as they were originally; the pain is usually described as lower in the abdomen and more to the left, without periodicity, and the relief of pain by food and alkalies is not so complete. Although hemorrhage from the stomach or bowel is not common with the secondary ulcer, when it does occur it is suggestive of ulcer, especially if there has been no bleeding before the first operation.

I know of only one case of perforation of a jejunal ulcer into the abdominal cavity. A gastrojejunostomy had been performed on this patient four years previously and he was completely relieved for some time. Four years later he was operated on elsewhere for an acute perforation of a jejunal ulcer. Wright reports that he found records of thirty-one acute perforations in 135 cases, and states that perforation is more common following anterior gastro-enterostomy than after posterior gastro-enterostomy.

I have been particularly interested in a group of cases in which the

ulcer perforated into the colon, forming a gastrocolic or jejunocolic fistula. Bolton and Trotter state that a trifle more than 10 per cent of jejunal ulcers become adherent to the colon and perforate into it. They

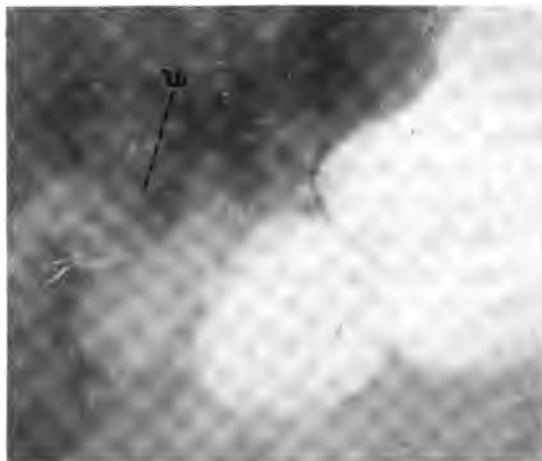


FIG. 69 (Case A160721).—Duodenal ulcer: *u* indicates the deformity due to ulcer.



FIG. 70 (Case A160721).—*s* indicates the deformity of the stoma due to jejunal ulcer seven weeks after operation for duodenal ulcer shown in Figure 69.

collected thirty-one such cases including four of their own. If the ulcer is in the jejunum the colon may easily come into contact with it, and as the ulceration extends it may perforate directly into the colon. How-

ever, in the six cases of colonic fistula in the series of 101 ulcers the perforation occurred more often when the ulcer was close to the mucosa of the stomach. In such cases the ulcer extends into the mesocolon so that it becomes involved in the ulceration and is greatly thickened and edematous. This later contracts and pulls the colon down on to the anastomosis and a fistula follows. In performing the primary operation this may be prevented by suturing the edges of the opening of the mesocolon well back on to the surface of the stomach and making the opening as near as possible to the root of the mesocolon so as to keep the colon well away from the suture line. The first intimation that the patient has of the existence of a fistula into the large intestine is a persistent diarrhea, the vomiting of fecal material, and belching of foul-smelling gas. If the fistula is large and especially if it is of the gastro-colic type, diarrhea is produced almost immediately after food is taken into the stomach, and the food is passed in much the same form that it was taken. Emaciation becomes marked very quickly. In one of our cases complete relief of all gastric symptoms was obtained by gastro-enterostomy and there was no suggestion of further trouble until five years later, when the patient was seized with an attack of persistent diarrhea. A roentgen-ray examination of the colon made a few minutes after a bismuth enema revealed a considerable portion of the bismuth in the stomach. In the other cases there was the usual history of jejunal ulcer for some time before evidence of a fistula into the colon. If the fistula is small and is between the jejunum and the colon, it may produce diarrhea and vomiting of fecal material at intervals; at other times the food is passed normally and the fistula seems to be closed.

DIAGNOSIS

Jejunal ulcer is always to be suspected when a recurrence of symptoms follows an interval of relief as a result of a gastro-enterostomy for ulcer. These symptoms may be the result of reactivation of the original ulcer, but in most instances they are due to a secondary ulcer. The development of malignancy must also be considered as well as an inflammation in the appendix or in the gallbladder. Roentgen-ray examination offers the most accurate method of differential diagnosis (Carman). A fistula into the colon may or may not be determined by the roentgen ray. In some of the cases in which a large fistulous opening was found at operation the opening had not been demonstrated by the roentgen ray, but a jejunal ulcer had been demonstrated.

TREATMENT

The possibilities of prophylaxis, I believe, have not been considered sufficiently in the treatment of jejunal ulcer. We must recognize the fact that it is not enough to perform a gastro-enterostomy and dismiss the patient without further treatment. Fewer secondary ulcers will occur if other foci of infection within the abdomen and the more commonly recognized areas for focal infection are eliminated. Reducing trauma to the tissues and dispensing with the use of nonabsorbable suture material will tend to reduce the number of these cases. No doubt we have all paid too little attention to the after-care, especially the diet. Cases are reported in which a secondary ulcer followed very soon after a gross indiscretion in diet. Much can probably be accomplished if the patient is restricted and kept under a certain régime for a certain time.

If jejunal ulcer is diagnosed and the symptoms are mild it is well to try medical management with the hope of obtaining relief, although in the Clinic usually we are not able to relieve these patients except by operation. Our experience leads us to believe that the best plan to follow at operation is to undo the gastro-enterostomy, excise the jejunal ulcer, close the opening in the stomach and intestine, excise the original ulcer, and at the same time perform a plastic operation on the pylorus if it seems best. In some instances it is necessary to reestablish the gastro-enterostomy or make a new one, but, if possible, this should be avoided because more ulcers may form in spite of all precaution.

In case a fistula has formed between the stomach and the colon or between the small intestine and the colon, the operation is liable to be tedious and difficult. A number of cases are reported in which it was necessary to excise a part of the jejunum, colon, and stomach, which makes a very formidable procedure. A large tumor is generally present at the site of the anastomosis, but it is made up of greatly thickened and edematous tissue. When a cleavage line is started in these tissues often the old anastomosis can be exposed, the colon separated, and the opening in it closed. The stomach and the jejunum may then be separated and these openings closed. This is much simpler than resection and should be done when possible. This plan was carried out in four of the six cases of fistula. In one a partial resection was required, and in one a complete resection. In one of the cases a gastroduodenostomy was made after the jejunal ulcer was excised.

RESULTS OF TREATMENT

The results of the operations in these cases of secondary ulcer have been reasonably satisfactory, especially since the importance of dispensing with the gastro-enterostomy whenever possible has been realized. If a secondary ulcer has once formed after gastro-enterostomy it is surprising how many will continue to form if the anastomosis is maintained in these patients who seem to have some definite irregularity or specific infection. In a few instances I have observed such repeated occurrence in spite of the fact that alkalization and systematic post-operative management were established and kept up from the time of the operation. Ballance mentions two cases in which alkalies did not prevent the occurrence. Nevertheless, I believe that proper management during the healing of the tissues following gastro-enterostomy and for some time afterward offers a great deal in the prevention of secondary ulcers.

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A TECHNIC FOR MAKING A BILIARY FISTULA*

FRANK C. MANN

Of the many methods described for making biliary fistulas one of the following procedures has been generally employed: (1) suturing the gallbladder to the abdominal wall and opening it so that bile drains to the exterior; (2) suturing a cannula or rubber tube in the gallbladder; (3) excising the common bile duct at the point of entrance to the duodenum with a piece of duodenal wall and suturing it to the skin; and (4) placing a cannula in the common bile duct.

All of these methods have been tried in our laboratory and have been found unsatisfactory in many ways. The most successful of these methods of making a biliary fistula we have found to be suturing the gallbladder to the skin. In many experiments the bile will drain through the gallbladder for a long time. Usually, however, the viscus becomes infected, which may seriously interfere with the results of the experiment. It should be noted that when the bile is drained through the gallbladder it is absolutely essential that the common bile duct is doubly ligated and sectioned. Even after such a procedure the partial re-establishment of bile drainage into the intestine is not uncommon. When cannulas are used they quite frequently ulcerate out or the area surrounding them becomes infected, making the work and results unsatisfactory. The transplantation of the duct with a piece of the duodenal wall is often a failure because of the poor blood supply to the transplanted tissue, because of the tension necessarily placed on the sutures and tissue which hold the duct stretched to the abdominal wall, and because of injury to the pancreas and infection. In order to overcome some of these difficulties another method was devised for the work in our laboratory and has proved very satisfactory. We have used it in the dog only, but it could be employed in other species, such as the cat and goat. The essentials of the technic are, first, definite fixation of the common bile duct in a superficial position before its relation to the duodenum is disturbed, and, second, draining the duct to

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the exterior. The operative procedure is carried out in two stages. In the first stage the duodenum is immobilized just under the skin in a manner so that the common bile duct is close to the surface. After complete healing has taken place the duct is exposed, the distal end ligated, and the proximal end left open, flush with the skin.



FIG. 71.—The first part of the duodenum pulled out into the wound and the peritoneum and fascia sutured through the openings made in the mesentery, thus fixing it firmly in position with the bile duct partially exposed.

Briefly, the steps of the operation are as follows: Under ether anesthesia and with sterile technic a midline or right rectus incision is made. The incision should be carried forward as far as possible without opening the pleural cavity. The pylorus and first portion of the

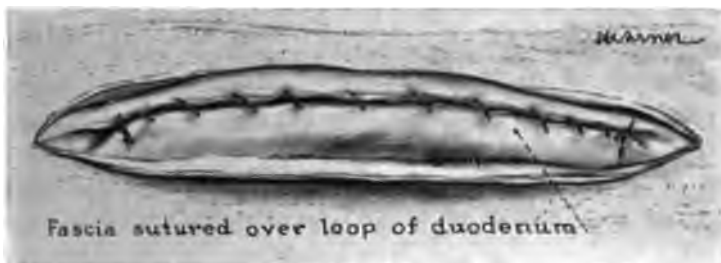


FIG. 72.—The subcutaneous fascia sutured over the transposed loop of the duodenum.

duodenum are located and pulled up into the wound. A small opening through the mesentery of the duodenum is made about 4 cm. on each side of the point of entrance of the common bile duct into the duodenum and between the duodenal wall and pancreas. Care must be taken in making these openings not to injure the pancreas and the blood vessels

going from the pancreas to the duodenum, and in making the lower opening not to injure the major pancreatic duct. Through these openings the peritoneum and, later, the fascia are sutured with double No. 2 chromic catgut. This procedure leaves the duct-bearing portion of the duodenum just under the skin (Fig. 71). The superficial fascia and the skin are then sutured over the transposed loop of intestine (Fig. 72). In closing around and over the upper and lower ends of the loop care must be taken not to cause too much pressure, as obstruction may be produced. After complete healing has taken place, which requires from seven to fourteen days, at a second operation a small incision is made over the point of the transposed loop where the common bile duct is located, the duct is exposed, ligated, and opened so that it will drain at its point of emergence from the skin. It is usually a good plan to keep a soft rubber catheter in the duct for the first day or two after operation. This prevents inflammation following operative trauma from obstructing the flow of bile. The operative wound usually heals quickly and in a very few days after the second operation observations can be started.

We have found this method of making a biliary fistula more successful and satisfactory than any other. By simply passing a catheter into the opened end of the duct observations can be taken on the secretory activity of the liver, the secretory pressure of the organ, or the movements of the gallbladder. We have made repeated observations on some of our animals for periods of six months or more, during which time the animal was maintained in an apparently normal condition. However, since bile seems to be an absolutely necessary secretion for the maintenance of life and good health, sooner or later all our animals have developed serious conditions regardless of the method of making a bile fistula or the method of feeding. As in all fistulas, there is a tendency toward a healing over of the opening, and for this reason it is desirable to catheterize quite frequently. The cicatrization is not so troublesome, however, as when the bile is drained through the gallbladder and after the first few weeks catheterization is not necessary.

POSTOPERATIVE BILIARY FISTULAS*

DONALD C. BALFOUR AND JAMES W. ROSS

Biliary fistulas are of great surgical interest because of their manifold causes, the variety of their communications, and the important problems connected with their surgical management. Two types occur, spontaneous and postoperative.

Spontaneous biliary fistulas are surgical curiosities because of the bizarre course which they may pursue. In finding an exit externally they may open at various points in the chest or abdominal wall, or even in the right thigh, but they usually open at or near the umbilicus, probably being directed to this point by the falciform ligament. Spontaneous fistulas may communicate internally with almost any part of the gastro-intestinal tract, a bronchus, the right kidney, or the urinary bladder; they may even perforate the pericardium. The rarity of spontaneous biliary fistulas and their curious communications constitute their distinguishing features; they are not included in the series on which this paper is based.

A postoperative biliary fistula which continues beyond the expected time limit, after an apparently successful operation on the gallbladder or ducts, is not only an annoyance to the patient, but is most disconcerting to the surgeon. Failure of the fistula to close spontaneously means that some obstruction prevents the bile from flowing in its normal course; that faulty surgery is probably responsible for the disturbing sequel; and that repair of the fistula may offer serious difficulties. Nor is the situation any less confusing for the surgeon called on to repair a fistula following an operation by another surgeon, for, although spared any responsibility for the fistula, perplexing factors have been added because of insufficient knowledge concerning the findings and details of the original and subsequent operations.

CAUSES OF POSTOPERATIVE BILIARY FISTULAS

A recent review of the 166 cases of biliary fistulas seen in the Mayo Clinic between January 1, 1910 and December 31, 1919, suggested the

* Reprinted from the Archives of Surgery, 1921, iii, 582-594.

publication of the series as a basis for some observations on their causes and surgical management. That gallstones and their complications are primarily the cause of postoperative fistulas in a large percentage of cases is a fact most apparent in this review (Table 1). The findings at operation, together with the historical data, show that in 85 per cent of the cases gallstones were directly or indirectly the causative factor. If one includes also the cases in which the original operations were carried out on the assumption that gallstones were present, although stones were not found at operation, the symptoms being due to cholecystitis, there remain only a very few cases in which the symptoms of gallstones did not play a primary part (Table 2).

Another obvious fact is that the gallbladder had been removed in only 10 per cent of the patients with chronic fistulas. The relative merits of cholecystectomy and cholecystostomy are now generally recognized, and the facts brought out in this series of cases emphasize these relative merits. It is reasonable to assume that by removal of the gallbladder at the first operation a large proportion of these fistulas could have been prevented. Cholecystectomy would have precluded a persisting fistula in the twenty-two cases of chronic cholecystitis; it would have eliminated the group of twenty-eight cases of "stones in the gallbladder," and it would have made the oversight of a stone in the cystic duct very unlikely. Moreover, a stone in the common duct is much more likely to be discovered by the surgeon who performs a cholecystectomy than by the surgeon who contents himself with a cholecystostomy. In cholecystostomy more risk of an incomplete operation or of overlooking a pathologic condition is involved than in cholecystectomy. To the latter operation is added the further danger of trauma to the hepatic or common ducts, although in a well conducted operation this danger is negligible.

Another point to be noted is that, considering the technical and anatomic difficulties often associated with secondary operations on the biliary tract, the group of cases in which the condition actually producing the fistula is listed as "undetermined" is remarkably small. The surgeon may wisely leave the condition undetermined if he finds that biliary function can be satisfactorily and permanently reestablished without a prolonged investigation which might involve additional risk and serve no good purpose.

PREVENTION OF BILIARY FISTULA

More important than the variety of conditions which produce fistulas is the question whether or not such a result could have been prevented at the original operation. Because of the margin of error always present in surgery of the gallbladder and ducts, the numerous and varied factors which contribute to an inadequate original operation, and the unknown incidence of stone reformation, it is doubtful if total elimination of postoperative fistulas can be attained. Taking all circumstances into consideration, however, and excluding malignancy and those cases in which a fistula is deliberately provided for, it would seem that the unanticipated occurrence of a postoperative fistula should be an exceedingly rare sequel to any operation on the biliary tracts. The incidence of such fistulas in the Mayo Clinic from 1910 to 1919 inclusive was 0.1 per cent, twelve in 9,009 operations on the gallbladder and ducts. Four of these twelve persistent fistulas, as shown by subsequent operation, were due to stone in the common duct, four to stone in the cystic duct, three to recurrent cholecystitis in a residual gallbladder, and one to stricture of the common duct following cholecystectomy. The most interesting fact concerning this group of twelve cases is that, with one exception, the last case mentioned, in no instance had the gallbladder been removed. A series of 5,997 cholecystectomies in the past ten years in the Mayo Clinic with but one subsequent fistula, compared with a series of 1,879 cholecystostomies with eleven postoperative fistulas, is a striking illustration of one advantage of cholecystectomy. Cholecystectomy not only invites more thorough exploration, but eradicates more efficiently potential and actual pathologic processes.

FACTORS IN THE PRODUCTION OF POSTOPERATIVE FISTULAS

Causes which lead to overlooking or producing conditions found to be diverting the bile through the fistula may profitably be considered. Surgical inexperience, inadequate exposure, an operation of intrinsic difficulty, a hurried operation, incomplete or careless exploration, failure to remove the gallbladder, accidental injuries of the ducts, and unintelligent use of drainage are the most apparent indirect causes, and are deserving of some individual comment.

Inexperience.—In surgery of the gallbladder and ducts inexperience takes a greater toll than in many other surgical fields. First, faulty

diagnosis may lead to ill-advised operation for cancer of the pancreas. Second, inexperience is responsible for failure to realize the significance of findings at operation, such, for example, as that clear colorless fluid in the gallbladder (so-called white bile) means obstruction of the cystic duct, or complete obstruction of the common duct, or that, even if a stone cannot be palpated, a dilated common duct is an indication for incision and exploration, especially if there is an associated history of jaundice. Third, the inability of the inexperienced operator to carry out safely such surgical measures as the removal of a soft stone from the ampulla of Vater or stones from the hepatic duct renders it difficult for him to accomplish desired results. Finally, if operative injuries, particularly of the ducts, are to be avoided, experience is essential.

Inexperience is a relative term, for, in all the problems of diagnosis and treatment which can arise in diseases of the gallbladder and ducts, it is impossible for any surgeon to become so efficient that further experience would not at times be beneficial to the patient. The results of gross inexperience, however, will probably be much less in evidence when medical graduates will be required to obtain the necessary post-graduate study before invading special surgical fields, and when hospital standardization reaches the plane on which it should rest. In the meantime, the patient who places himself in the hands of the inexperienced surgeon is fortunate if that surgeon realizes his limitations and does not attempt more advanced surgery than these allow.

Inadequate exposure.—The master word in the craft of surgery is simplicity (Moynihan). One of the most common mistakes made by surgeons is the failure to appreciate the importance of good exposure in contributing to the simplicity in operation. How frequently may be recalled operations made unnecessarily difficult by a small incision, poor light, and an obscured operative field. Nearly all the serious situations in operations on the thyroid, spleen, kidney, pelvic organs, and so forth, are associated with difficult accessibility. In surgery of the gallbladder, accessibility is sometimes particularly difficult, and the same operative procedure may entail the widest limit of difficulty or facility.

Disastrous sequelæ may be directly attributable to inadequate exposure, and we may appropriately refer briefly to the more important means of securing the best possible exposure. A suitably placed

incision of sufficient length is essential. In the Mayo Clinic we have adopted a modified Bevan incision in the rectus beginning high in the epigastrium and about 1.25 cm. to the right of the middle line; such an incision gives the most adequate access to any lesion that may be encountered in the gallbladder or ducts. The incision in the skin and subcutaneous tissues should sufficiently exceed in length the proposed opening in the aponeurosis, muscle, and peritoneum, so that, should enlargement of the opening in these deeper layers become necessary as the operation proceeds, it would not be necessary to extend the incision in the skin or subcutaneous tissues. A capable first assistant can be of great service in drawing away from the field of operation the hepatic flexure of the colon, the duodenum, and the pyloric end of the stomach. Masson has recently suggested a most useful means of gaining better view and access. He introduces a large gauze pack between the superior and outer aspects of the right lobe of the liver and the diaphragm, so as to swing and rotate the liver downward and forward, gaining in this way not only better access to the gallbladder and ducts, but lessening the excursions of the liver during respiration.

An operation of intrinsic difficulty.—Even with every aid, the difficulties inherent in the individual operation may be considerable because of a fleshy patient, a high-lying liver, inflammatory thickening of the gallbladder, ducts, and pancreas, or adhesions, which prohibit a satisfactory exposure. Moynihan has recently stated that he knows of nothing in surgery which approaches in difficulty a cholecystectomy under such circumstances. The conditions may be sufficient to leave doubt in the surgeon's mind as to whether the full extent of the pathologic processes have been determined and dealt with; usually, however, the subsequent course of the patient shows this fear to be unfounded. There are cases in which failure to deal with the conditions which later are responsible for the continued draining of bile can be fairly attributed to anatomic and pathologic obstacles, and a persisting fistula may also follow an unusually difficult operation on the deep ducts, such as resection for cancer, cyst, or stricture, or a reconstructive operation for existing fistula.

Hurried operations.—It is hardly necessary to comment on the dangers of a hurried operation. Speed is responsible for many mistakes in abdominal surgery. What appears to be a brilliantly executed operation may in reality be quite incomplete through overlooking additional lesions. When operations on the gallbladder are followed by

unfortunate sequelæ and discreditable results it is usually because they have been carried out on insufficient indications or because important details have been sacrificed to haste.

Incomplete or careless exploration.—A thorough exploration is one of the most important principles in abdominal surgery, and in the abdomen no region demands so much care and efficiency in exploration as does the biliary tract. Every means, inspection, palpation, and instrumentation should be utilized. If, for example, small nodules are palpated in the line of the cystic duct, and a differentiation of glands and calculi cannot be established with certainty by inspection and palpation, exploration should be continued by splitting the gallbladder down to the opening of the cystic duct, so that by instrumentation it can be determined whether the palpable nodules are within or without the duct. Similarly, when doubt exists concerning the patency of the common or hepatic ducts (occasionally careful inspection and palpation of ducts fails to convince even the most skilled surgeon that the ducts are clear), incision of the main duct and exploration with probe and scoops are imperative. The marked similarity under palpation between cancer of the duct and stone should not be forgotten. Exploration of the pancreas involves difficulties in the differentiation of various degrees of pancreatitis, of the nodular form of pancreatitis, and of cancer. In such cases, particularly if obstructive jaundice exists, a correct differentiation is extremely important, both from the standpoint of operative procedure and from that of prognosis. Fortunately, such differentiation can usually be made at operation.

Uncertainties may remain after most efficient exploration; on the other hand, a most obvious pathologic condition is sometimes overlooked by neglect or carelessness in exploring. Such oversight is doubtless partly due to the assumption that a gallbladder filled with stones is sufficient and satisfactory evidence to support the history, and that the removal of the stones should assure the patient complete relief. A diligent, routine search for surgical conditions in other portions of the biliary tract is accordingly omitted, frequently to the continued and later disability of the patient. An incomplete operation may thus be, and usually is, the primary cause for a persistent fistula, the most common mistake being failure to remove all the stones from the cystic, common, or hepatic ducts. In this series there were 105 such cases. Rare conditions, such as a ruptured gallbladder with localized abscess and beginning peritonitis, occasionally justify incomplete

operation in anticipation of dealing radically with the pathologic process at a later and safer time.

Failure to remove the gallbladder.—A contributory factor to post-operative fistula in 90 per cent of the cases in this series was failure to remove the gallbladder at the first operation; doubtless the removal would have spared these patients the second operation. Comparative statistics of experienced surgeons show that cholecystectomy has a decided superiority over cholecystostomy in every respect, operative mortality, immediate and late results, and biliary function.

Accidental injury to ducts.—Under this heading may be included the most serious conditions with which the surgeon has to deal. In several recent articles the common types of such injuries, the causes of their occurrence, and suggestions for their avoidance have been discussed. The most important injury is division, crushing, or resection of a portion of the common or hepatic ducts. The chief cause for such accidents in the operation of cholecystectomy lies in failure accurately to indentify the cystic duct. The various anomalous relations which the cystic duct may hold to the hepatic and common ducts may easily lead to damage of the deeper ducts if the cystic duct is not carefully isolated before it is clamped and divided. Careless or hurried attempts to grasp a bleeding cystic artery (especially if it has retracted into a position close to the hepatic duct) may result in clamping and ligating the hepatic or common duct.

Unintelligent use of drains.—In no case of the series was there clear proof that the pressure of a drain was solely responsible for the fistula. It is quite conceivable, however, that conditions productive of fistula could be brought about by gauze becoming adherent to the wall of the common duct already injured by pressure of a stone or by forceps. One case illustrates the fact that drainage, prolonged far beyond the reasonable time, may be sufficient to establish a permanent drainage tract. The tendency of late is to use less and less drainage in surgery of the gallbladder and ducts, and, indeed, in general abdominal surgery. In selected cases of cholecystectomy drainage may safely be omitted. In 236 cases observed during the last three years the results of such procedure have been satisfactory.

Reformation of stones.—Finally, in those cases in which the fistula closes for a varying time after operation and then reopens, the formation of stones must be mentioned as a possible factor, and in some instances apparently as the sole factor. In Table 1 is given the average length

of time fistulas had been present in the various types of cases, the average varying from four and one-half months in cancer of the pancreas to thirty-seven months in cases of "stones in the gallbladder." Why such a difference of time should exist in these groups is readily understood. It is not easy to explain, however, since the question is chiefly one of the reformation of stones, why such long periods intervened in some cases before the reopening of the fistula which had closed normally after operation. It may be accepted that stones can remain in the gallbladder many years without producing sufficient obstruction to reopen the drainage tract to the surface; but it is difficult to believe that a stone could remain long in the common duct without sufficiently raising the pressure of bile to divert it through its former external communication, or to cause symptoms sufficient to indicate its presence or to necessitate operation. Available evidence supports the view that when the original operation is thoroughly carried out, actual reformation of stones in any portion of the biliary tract is exceedingly rare, but it may occur in the gallbladder, or in a common duct even if the gallbladder has been removed. The tendency to the reformation in the common duct is greater in cases in which there has been long continued dilatation and infection from an obstructing calculus. Following the removal of such a stone the duct may become plugged with a soft type of pigmented stone which does not contain cholesterol, and a secondary operation becomes necessary within a few months. In three cases such stones have reformed a third time, and have been removed. A cure finally resulted in all.

Although it is seldom possible to attribute definitely the conditions which produced fistula to any certain one of the causes which we have just discussed, it should be emphasized again that in only sixteen cases in the entire series had the gallbladder been removed at the original operation, and, exclusive of the cases of operative injuries to ducts, in only three cases had cholecystectomy been performed.

INDICATIONS FOR SURGICAL INTERVENTION

The indications for the operative repair of a fistula to a large extent depend on the length of time the fistula has been draining, on its behavior from day to day, and on the cause and probability of its persistence. It is fortunate that there is no objection to allowing ample time for a fistula to close spontaneously. The general health of the patient is

not seriously disturbed, nor is the operation made more difficult by continued drainage, so that the hope that it will cease of itself justifies postponement of operation for a reasonable time.

When some portion of the biliary tract has been left open, such a wide variation exists, under normal conditions, in the duration and quantity of drainage that unnecessary apprehension is sometimes occasioned by continuance of drainage much beyond the usual time limits. The reason for such variation has not been determined. Apparently it does not depend on the operation, for in choledochotomies, for example, after the tube in the common duct has been removed, bile drainage ceases immediately in some cases, and in others lasts for days. A probable reason for such variability may be found in the character of sphincteric control at the ampulla. Because of such normal variability no very definite time limit can be laid down as a basis on which to determine the wisdom of surgical interference. A study of the postoperative records of the Mayo Clinic, however, shows that bile drainage rarely persists beyond three weeks after the last drains have been removed. If at the end of that time a large quantity of bile is continuously draining through the incision and only a small amount is entering the intestine, it may well be suspected that some mechanical obstruction exists, and that this obstruction will not of itself disappear.

In cases in which the drainage entirely ceases and then reappears, recurrence of discharge is frequently preceded by attacks of pain and jaundice, with possibly chills and fever, all of which disappear after the drainage tract reopens. Recurring fistulous activity, accompanied by such signs and symptoms, is almost a certain indication of obstruction of the common duct by a ball valve stone. It should not be forgotten, however, that obstruction of the common duct by cancer of the head of the pancreas may be temporarily and sufficiently relieved to permit passage of bile into the intestine, with consequent closure of the fistula for a short time. The alternate closing and opening of a fistulous tract may also be a manifestation of stone obstructing the cystic duct or the pelvis of the gallbladder. In such cases the signs and symptoms preceding reactivity are limited to pain, local soreness, and possibly a tender palpable gallbladder, while a discharge of mucus, possibly slightly tinged with bile, is further definite evidence that the gallbladder is shut off from the remainder of the biliary tract.

What length of time external drainage of bile may continue without

evident effect on the general health of a patient is an interesting question. In this series the longest reported period that a fistula had existed was eleven years; in this instance all the bile had not been diverted to the surface. The longest time during which all of the bile drained to the surface was three years. In this case at the third operation four stones, each about 3 cm. in diameter, were found in the common duct. Following a cholecystostomy elsewhere three years previously bile had drained copiously and the stools had almost continuously been clay-colored. A tube had been in place for two years. There was no jaundice; the hemoglobin, however, was only 35 per cent at the time of operation. The patient showed neither definite disturbance in gastrointestinal function nor recognizable nutritional disorder other than anemia. In another patient with stone in the common duct apparently all the bile drained to the surface for eighteen months. The longest periods of drainage in cases of injury to the duct were twenty-one months and twelve months (Table 3).

Preoperative diagnosis is always desirable, and we have already indicated some of the points on which a diagnosis may be established. In certain cases, especially when malignancy is suspected in the pancreas or in the duct or liver, a preoperative diagnosis is essential to the best interests of the patient. In cases of doubtful diagnosis operation may well be deferred, since the further course of the disease will settle the question. Sometimes the history of symptoms leading up to the original operation, in particular, the development of painless jaundice, associated with steady, progressive emaciation, together with the findings reported at operation, will give reasonable certainty to a diagnosis of malignancy and will justify advice on that assumption. If it is known that the common or hepatic duct has been injured, or if injury is suggested by a history of repeated operations, the surgeon must decide whether he should undertake one of the most difficult of all abdominal operations, namely, restoration of biliary function by reconstruction of the ducts.

SURGICAL TECHNIC

The operative management of biliary fistulas varies within wide limits. The cure of gallbladder fistula by removal of a stone impacting the cystic duct is quite simple and satisfactory. On the other hand, nothing can exact more surgical ability and experience than an attempt

to restore the normal course of bile after several previous efforts have been made to repair the ducts.

By avoiding adhesions in the field of the former operation it is surprising how much the operation for repair of a fistula may be simplified. This is accomplished by placing an incision beginning in the costosternal angle well to the median side of the former incision and the site of the discharge. Such an incision gives also much more direct access to the biliary ducts, which, regardless of preoperative findings, must always be thoroughly explored. The advantage of approach to the common duct through the upper end of such an incision is so great that, even though several prolonged operations to discover the cause of the fistula have previously been performed, a common duct stone may often be located and removed with ease. Location and removal of overlooked calculi, which are the commonest single cause of persistent fistulas, can easily be effected without much difficulty. If the gallbladder has not been removed, its early separation from the abdominal wall will facilitate the exploration and the steps of the operation. Before a complete examination of the operative field has been made the gallbladder should not be removed, for it serves a most valuable purpose when irreparable damage has been done to the common duct. or when there is malignancy in the duct or pancreas. Further, if it seems likely, but not certain, that a permanent and satisfactory repair can be made of a strictured common duct, the conservation of the gallbladder anticipates a possible recurrence of stricture in the duct, and, by means of subsequent anastomosis, provides a way for the diversion of bile to the gastro-intestinal tract directly through the gallbladder. When such an anastomosis becomes necessary, the stomach or duodenum may be made use of equally well. With the exception, then, of a very few cases in which the preservation of the gallbladder is justified for reasons mentioned, the organ should be removed because of its disposition to cause future trouble.

A satisfactory method of cholecystectomy, such as that described by Judd, should include as its most important feature the accurate identification and isolation of the cystic duct. When the gallbladder has been previously removed, its usefulness as a guide in operation will be missed. In ordinary cases, however, the absence of the gallbladder is not of consequence, for as a guide its place is well taken by the gallbladder notch of the liver.

In a patient who has already had the gallbladder removed, who

has had one or more reconstructive operations on the ducts, and who suffers from chronic jaundice with its attendant liver and blood changes, the repairing of a biliary fistula due to an extensively damaged or excised common or hepatic duct offers the most difficult situation which may confront a surgeon. Experience in the Mayo Clinic has demonstrated that the most satisfactory method, and in many instances the only method, of dealing with such cases is to make a direct anastomosis between the hepatic duct and the duodenum. This method, the principles of which were first described by W. J. Mayo in 1905, is so successful that the operation of hepaticoduodenostomy can be regarded as serving the same excellent purpose as cholecystogastrostomy or cholecystoduodenostomy when the gallbladder is present. The technic of hepaticoduodenostomy at present preferred and practised in the Clinic has been described in a recent paper.¹ The method is characterized chiefly, first, by the use of a duodenal flap (as originally advocated by Walton) which is wrapped around the posterior aspect of the stump of the hepatic duct, thus forming a trough for the duct; second, by a large opening in the duodenum; and third, by the consequent closing of the duodenal opening by fixation to the capsule of the inferior surface of the left lobe of the liver. The large duodenal opening and the manner of closing it prevents subsequent contraction on the end of the duct, with the intermittent or chronic jaundice which so frequently complicated former methods of uniting the hepatic duct and duodenum. When direct union of a severed common duct, or excision of a stricture, neoplasm, or cyst of the duct is necessary, one of the methods described in detail by Eliot may be employed.

RESULTS

In this series of operations in 166 cases of biliary fistulas there were sixteen deaths in the series, a mortality of 10 per cent. In operations undertaken for various conditions which were responsible for fistulas, the percentage of deaths shows very clearly the relative risks which accompany these operations. For instance, in the thirty-five cases of stone in the cystic duct no operative mortality occurred, while in the groups "division of the common duct" and "stricture of the common or hepatic ducts" six deaths in twenty-one cases were due largely to chronic jaundice and sequelæ so common in such cases. The general rate of 10 per cent mortality for the entire group is unfortunate when

compared to that of from 1 to 2 per cent which accompanies adequate primary operations on the gallbladder and ducts. Ten per cent mortality can, however, not be looked on as excessive for a group of cases so frequently presenting such serious surgical complications. In considering ultimate results, the first question, of course, is, what degree of success has attended the primary purpose of the operation, the closure of the fistula. Of the eighty-three living patients from whom we have been able to secure positive information, eighty (98 per cent) have been completely relieved of fistula. The health of patients who have reported is generally good, exceptions being chiefly confined to patients undergoing reconstruction operations on the deeper ducts. Of the entire series of patients, twelve reported occasional attacks of pain and jaundice; these were distributed as follows: "stone in the common duct" five; "stone in the cystic duct" two; "division of the common duct" two; "stricture of the common duct" two; and "stricture of the cystic duct" one. As a final observation, it may again be noted that, exclusive of the thirteen cases of duct injuries, in only three of the remaining 153 cases had the gallbladder been previously removed.

This review of the series of 166 cases of postoperative biliary fistula has shown, (1) the variety of conditions which may be responsible for persisting fistula, (2) the more common causes for the presence of such conditions, (3) the duration of some fistulas, (4) the surgical management of fistulas, and (5) the excellent results obtained by radical surgical measures.

TABLE 1
BILIARY FISTULAS

Proved cause of fistula.	Cases.	Gallstones found at first operation.	Gallbladder not previously removed.	Gallbladder previously removed.	Average duration of fistula.	Maximum duration of fistula.	Minimum duration of fistula.	
Stone in the common duct.	41	26	41	0	12.4 months	4 years	1 month	
Stone in the cystic duct.	35	25	35	0	24.5 months	9 years	3 weeks	
Stone in the gallbladder.	28	14	28	0	37 months	11 years	3 months	
Stone in the hepatic duct.	1	1	1	0		11 months		
Recurrent cholecystitis in residual gallbladder.	22	12	22	0	10 months	3.5 years	2.2 months	
Division of the common duct.	13	8	3	10	10.8 months	5 years	1 month	
Stricture of the common or hepatic duct.	8							
Stricture of the cystic duct.	3	11	9	8	3	18 months	7 years	2.5 months
Cancer of the gallbladder.	2	1	2	0	9 months	1 year	6 months	
Cancer of the pancreas.	4	2	3	1	4.5 months	7 months	10 weeks	
Chronic pancreatitis.	4	1	4	0	5 months	9 months	11 weeks	
"Cirrhosis of the liver".	1							
Hepatitis and infected hematoma.	1	3	0	3	0	9 years	1 month	
"Prolonged tube drainage".	1							
Indeterminate.	2	1	0	2	3.5 months	5 months	2 months	

TABLE 2

CASES IN WHICH STONES WERE NOT FOUND, BUT MAY HAVE BEEN PRESENT AT ORIGINAL OR SUBSEQUENT OPERATIONS

Cases.....	26 (15.7 per cent).
Stricture of the common or hepatic duct.....	2
Division of the common duct.....	5
Recurring cholecystitis.....	10
Chronic pancreatitis.....	3
Cancer of the pancreas.....	2
Cancer of the gallbladder.....	1
Cirrhosis of the liver.....	1
Hepatitis.....	1
Indeterminate.....	1

TABLE 3

PROLONGED DRAINAGE OF ALL BILE* TO THE SURFACE
(THIRTY-FOUR CASES)

Causative factors:	Cases.
Stone in the common duct.....	10
Division of the common duct.....	12
Stricture of the common duct.....	6
Cancer of the pancreas.....	3
Chronic pancreatitis.....	2
Stone in the hepatic duct.....	1

Average duration of complete fistula, seven months.

There was a total of ninety-three operations in this group (here and elsewhere, including primaries).

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* It is obviously difficult to establish absolute evidence of complete fistula (all bile). The evidence was carefully considered and only those cases that were fairly certain were included.

THE RELATION OF THE LIVER AND THE PANCREAS TO INFECTION OF THE GALLBLADDER*

E. STARR JUDD

Cholecystitis is nearly always associated with a certain grade of hepatitis or pancreatitis, or both. The degree of inflammation in the liver and in the pancreas is often so slight that it is recognized with difficulty. Cholecystitis does not always mean that the infection in the liver and pancreas will also be severe. In certain cases the disease seems farther advanced in the liver or pancreas than in the gallbladder, suggesting that it was primary in the liver or pancreas and secondary in the gallbladder. It is possible that infection may progress in this manner, nevertheless, all the evidence indicates that the infection is primary in the gallbladder. Graham has recently called attention to the intimate association between the gallbladder and the liver through the lymphatics, and has suggested that in certain cases the gallbladder may be infected through the lymphatics from the liver. A study of these lymphatics was made by Sudler some years ago, but their importance in relation to cholecystitis and hepatitis has not been realized until recently.

The gallbladder, as a part of the excretory mechanism of the liver, is brought into relationship with the liver through the bile ducts, thus it is possible, although not likely, for infection in the hepatic tissues to reach the gallbladder by way of the bile stream. Infection might pass through one viscus to the other through the venous system.

The gallbladder and the pancreas are also associated through the lymphatics and the bile ducts. It has been shown that the efferent lymphatics from the gallbladder and those from the pancreas anastomose around the head of the pancreas, and it has been further suggested that this is the reason why this part of the gland is most often

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invaded (Maugeret). Deaver believes that chronic pancreatitis in the majority of cases is due to the invasion of the substance of the gland by way of the lymph channel. He calls this condition pancreatic lymphangitis and says that it precedes interstitial pancreatitis. He believes that the source of this infection is the infected bile and the diseased gallbladder and in a few cases gastric and duodenal ulcers.

Opie, Meltzer, and Mann have shown that the bile entering the pancreatic duct under certain circumstances results in an inflammation of the gland similar to that of interstitial pancreatitis. Several years ago Archibald called attention to the fact that bile might be forced into the pancreatic duct as a result of the spasmodic contraction of the sphincter muscle at the end of the duct. He further suggested that remedies to overcome this would relieve the pancreatitis. Knowing that removal of the gallbladder cures most patients who have cholecystitis and pancreatitis, Mann and I removed the gallbladders from animals in order to study the changes which occurred as a result of the loss of this organ. Apparently there was an attempt to compensate for the loss of the functions of the gallbladder. The first change was dilatation of the common duct, and the second paralysis of the sphincter at the entrance of the duct into the duodenum. This seemed to explain why removal of the gallbladder relieved inflammation in the pancreas, if it were due to an influx of bile the result of a spasmodic condition of the sphincter muscle. If it were due to an extension of infection from the gallbladder through the lymphatics, then naturally removal of the infected gallbladder would afford relief.

The mechanism of the excretory apparatus of the liver is not altogether understood. The gallbladder seems to have several important functions and yet when it is destroyed or removed these are well compensated for by changes in the bile ducts, and in the operation of the control sphincter at the end of the common duct. So far as we can determine no serious consequences follow loss of the gallbladder. We have many patients under observation from whom the gallbladder was removed years ago, and nothing abnormal can be detected, no gross or microscopic changes in the liver or pancreas result.

ENTRANCE OF BILE INTO PANCREATIC DUCTS

It has been shown that pancreatitis may result from the injection of bile into the pancreatic ducts. Mann has recently performed a

series of experiments to determine the conditions under which bile must enter the ducts in order to produce this change in the gland. He divided his work into several studies and investigated the cause or causes of pancreatitis, both acute and chronic, with special reference to the bile. He found that in the goat the pancreatic duct empties directly into the common bile duct several centimeters from the entrance of the latter into the duodenum. This offers an ideal natural anatomic condition as a means of determining whether there is a physiologic mechanism which can, under sufficient pressure, force bile into the pancreatic duct and produce pancreatitis. Accordingly the common bile ducts in five goats were doubly ligated and sectioned distal to the entrance of the pancreatic duct, and the animals were allowed to live for various lengths of time. None developed acute pancreatitis and none died from the effects of the bile being forced into the pancreatic duct, although bile was forced into the pancreatic duct; this was easily demonstrated in two animals that lived for three or four weeks after the operation. In both the pancreas was stained greenish throughout, and the pancreatic ducts were dilated and filled with a greenish fluid. On abrasion of the pancreatic surface bile could be forced through by pressure on the gallbladder; and while the pancreas showed well marked pancreatic changes, the changes simulated more nearly those following duct occlusion than those following the injection of bile. Many observers have demonstrated that in a large number of experiments the injection of bile into the pancreatic duct with a syringe produces acute hemorrhagic pancreatitis. However, injecting a fluid such as bile with a syringe under very high pressure causes a definite trauma to the gland. Mann, therefore, conducted experiments to determine the maximum pressure that could be developed in the common bile duct.

The pressure in the common bile duct is due to three factors: the secretory pressure of the liver, the contractile pressure of the gallbladder, and the mechanical pressure on the liver and biliary ducts by the abdominal muscles and the diaphragm. The maximum pressure produced in the common bile duct, the result of a combination of all these factors, was studied and attempts were made to analyse the component parts of each. The experiments were performed on dogs with permanent biliary fistulas, that is, through an especially devised technic the common bile duct was transplanted to the skin and the pressure recorded by passing a catheter into the common duct and

connecting by means of a "T" tube to a straight glass tube and the pressure then recorded in terms of millimeters of bile. The animals thus operated on and studied were quite comfortable, and many observations were made extending over long periods. These observations demonstrated:

1. The secretory pressure of the liver is seldom greater than 350 mm. of bile.

2. The contractile pressure of the gallbladder is difficult to estimate, but in no instance could it be determined that it was any greater than the maximum secretory pressure of the liver. As a matter of fact it is questionable whether the gallbladder ever contracts and produces pressure greater than 300 mm. of bile. There seems to be no doubt that the gallbladder has a contractile mechanism exerting pressure on the biliary tract, but the contractile power of its own intrinsic muscles has been greatly overestimated.

3. The mechanical effect of the abdominal muscles and of the diaphragm on the liver is the most marked in producing changes in the intraduct pressure. Deep respiratory movements and struggling produce greater fluctuations in pressure in the common bile duct than is possible by the secretory pressure of the liver or by contraction of the gallbladder.

Thus far Mann has found only one condition, the act of vomiting, under which the pressure in the common bile duct is greatly increased. If the animal is made to retch the intraduct pressure increases enormously, reaching as high as 1000 mm. of bile. After having determined the maximum pressure that can be exerted on the bile in the common bile duct, Mann investigated the effect of the injection with a syringe of bile into the pancreatic duct under such a range of pressures. As has been stated, if bile is injected into the pancreatic duct with a syringe, acute pancreatitis usually occurs, and quite frequently the outcome is fatal. If bile is injected under pressure of 500 mm., or a pressure greater than the secretory pressure of the liver and the contraction of the gallbladder, acute pancreatitis does not occur. If the bile is injected under a pressure of 1,000 mm., which was the maximum pressure produced in the common bile duct, namely, that produced by vomiting, acute pancreatitis may occur, although rarely. From this Mann concludes that even if a stone or the action of the sphincter should convert the pancreatic and common bile ducts into a continuous channel, only under exceptional conditions, such as struggling or

vomiting, would it be possible to inject bile into the pancreatic duct under sufficient pressure to produce pancreatitis.

In order to determine whether it would be possible for the sphincter to convert the common bile duct and the pancreatic duct into a continuous channel, as has been suggested by Archibald, the sphincter at the end of the common bile duct was examined in four species in which the two ducts enter together, namely, the dog, the cat, the monkey, and man. The examination of several hundred sections of the sphincter showed clearly that in almost all instances the muscle fibers are intimately connected with both ducts, so that a contraction of the sphincter will simultaneously close both the common bile duct and the pancreatic duct and will not convert them into one continuous channel. However, in two instances, in cat and in man, considerable muscle tissue has been found distal to the point of common entrance of the two ducts, so that there is a vague possibility that contraction of the sphincter might allow bile to be forced into the pancreatic duct.

The relation of the common bile duct to the pancreatic duct was studied in 170 patients for the purpose of determining the percentage of instances in which the anatomic arrangement was such that it would be possible for either a stone or the action of a sphincter to convert the two ducts into one continuous passage way. This seemed a possibility in only 4.5 per cent. From this data it may be concluded that:

1. Only exceptionally is there a physiologic mechanism which can inject bile into the pancreatic duct with sufficient force to produce pancreatitis.

2. Only very exceptionally is there an anatomic arrangement whereby the ducts can be converted, either by a stone or by the action of the sphincter, into a continuous passage way permitting bile to flow from the common duct into the pancreatic duct.

3. While there is no doubt that pancreatitis is sometimes due to or associated with the passage of bile into the pancreatic duct, our data tend to support the hypothesis that the number of such instances must be exceedingly small.

If Mann's conclusions regarding the bile factor in the etiology of pancreatitis are correct it would seem that, in most cases at least, we must search elsewhere for the cause. It will most likely be found, as Deaver says, in the extension of infection to the pancreas through the lymph channels.

In this experimental work we must take into consideration the

fact that the bile which regurgitates into the pancreatic duct is normal bile and has not been changed by infection. It is possible that the infection in cases of cholecystitis changes the bile so that it readily causes trouble in the pancreas. Archibald has shown that infection reduces the protecting power of the mucus.

CHOLECYSTITIS ASSOCIATED WITH HEPATITIS

In a number of instances during operations in cases of pancreatitis we have removed small pieces of tissue from the pancreas for study. This was done particularly if diabetes was present. Nicoll carried out the same procedure in a series of cases. The information obtained thus far has not aided in studies to determine the cause of pancreatitis.

Hepatitis does not always greatly change the gross appearance of the liver and often cannot be recognized except microscopically. The liver may be slightly enlarged, although the enlargement is detected with difficulty even on careful observation. Kehr estimates the enlargement 15 per cent and Graham 87 per cent. It has seldom been observed in our cases. In some instances there is apparently an edema in the hepatic tissues, which causes a rather rounded liver edge, but in most cases the edge is sharp. The surface in the region of the gallbladder is whiter, often mottled, with numerous white dots and lines. The inflammation of the liver is characterized by a leukocytic infiltration of the interlobular or periportal sheaths. This may progress to the stage of necrosis and fat infiltration, and in the more chronic cases may present the picture of early cirrhosis. The clinical manifestations are not clear cut and are probably obscured by the inflammation in the gallbladder.

In our necropsy studies we have observed that hepatitis is always found in association with gallbladder and bile tract infections and is never seen in association with ulcers of the stomach and duodenum or inflammation of the appendix.

With the idea of learning the part played by inflammation of the liver I recently reviewed the histories of 1,290 gallbladder cases in which operation had been performed in 1919. The operations were performed by ten surgeons in the Clinic, and the observations on the degree of hepatitis and pancreatitis probably varied with the individual surgeon's particular interest in the conditions.

Forty-seven cases of cholecystitis with hepatitis were chosen for

study. In many of these a piece of liver tissue was excised for microscopic study at the time of the operation. There were undoubtedly many other cases of hepatitis in the series, but in some the inflammation was so slight that it was not recognized; other cases were ruled out from this study because of complications.

A careful review of the clinical histories did not reveal anything suggesting involvement of the liver. Each contained a more or less typical history of cholecystitis. The average duration of symptoms was nine years. The longest duration was thirty-two years and the shortest three months. There were stones in the gallbladder in twenty-two of the forty-seven cases, and in the common duct in three cases. Slight jaundice was present in five cases, and without the evidence of biliary cirrhosis which is found in the obstructive cases. The gallbladder was removed in forty-one of the cases and drained in two; the common duct was also drained in six cases. The regional lymphatic glands were markedly enlarged in seven cases; they were undoubtedly somewhat enlarged in many others. The liver was estimated to be greatly enlarged in three cases. No attempt was made actually to measure the liver and it may have been somewhat enlarged in many more cases. Both pancreatitis and hepatitis were associated in fourteen of the cases.

All of the forty-seven patients recovered satisfactorily from the operation, and we have been able to trace twenty-eight. Twenty-four are practically well, four were not greatly benefited and have since had similar attacks. It is more than one year since the operation, which would seem sufficient time for complete restoration of the liver, so it is quite probable that the present symptoms are not due to hepatitis.

Besides these forty-seven cases there were thirty-one in which the changes in the liver had advanced to cirrhosis. The cirrhosis was not suggested by the clinical features. Pancreatitis was associated in twelve of the thirty-one cases. In spite of the diseased liver and pancreas seventeen of the eighteen patients we have traced report that they have been practically well since the operation for cholecystitis. Two patients have not thus far improved. Since the large percentage of the patients are improved as a result of the treatment the hypothesis seems to be sustained that cholecystitis is the primary lesion and treatment for it also relieves the infection in the liver.

Of the total number of 1,290 gallbladder and bile duct cases, 347 (26.8 per cent) had associated pancreatitis. For a comparative study

of the cases of cholecystitis with hepatitis and cirrhosis, we selected forty-eight cases of cholecystitis with pancreatitis. The clinical histories in such cases do not as a rule suggest pancreatitis. The condition was determined at the time of operation by enlargement in the pancreas, more frequently in the head; in others the pancreas was generally hardened. On palpation it was found to be more firm than normal and the lobes and lobules could be felt as separate pieces of gland. Often an irregular rough surface, frequently with a sandy or shot-like feel, could also be palpated. Edema was often present. Thirty of the forty-eight patients have been well one year after the treatment of the gallbladder disease; two are not improved. No reply was received from letters of inquiry to sixteen.

Stones were present in the gallbladder in forty-six cases and in the common duct in eight. The common duct was drained in fifteen cases. While the lymphatic glands were undoubtedly enlarged in many cases, they were noted only in six. This does not mean that more of these cases were not cases of pancreatic lymphangitis, but simply that the lymph nodes were not large enough to attract attention.

DISCUSSION

1. A review of our studies inclines us to believe with Graham that cholecystitis rarely exists without hepatitis. Often the inflammation in the tissues of the liver is so slight that it is not noticed unless special effort is made to detect it. The close association of the liver and the gallbladder by the lymphatics makes extension of the infection from one to the other very easy.

2. Pancreatitis occurs frequently with cholecystitis, and as a result a definite gross change occurs in the pancreas. While it is possible that the inflammation in the pancreas may be due to the influx of bile into the pancreatic duct, Mann's recent experiments show that this does not occur except under unusual conditions. It is possible for infection to invade the pancreas by way of the lymphatics from the gallbladder, and in many cases this probably explains the source of the infection. It is apparently entirely relieved by the treatment for the cholecystitis.

3. We were unable to find in the clinical histories of patients known to have hepatitis any symptoms that were especially suggestive of the inflammation. The same may be said of the patients in whom the liver changes had progressed to a stage of cirrhosis.

4. It is possible that the incomplete relief from symptoms and the recurrences in a small number of these cases are due to inflammations in the liver or pancreas.

TABLE 1
CHOLECYSTITIS WITH PANCREATITIS

(Forty-eight Cases)		Years.
Average age of patients.....		42
Oldest.....		66
Youngest.....		22
Longest duration of symptoms before operation, forty years.		
Shortest duration of symptoms before operation, two months.		
	Operations.	
Cholecystectomy.....		48
Choledochostomy.....		15
Appendectomy associated with other operations.....		35
Gastro-enterostomy associated with other operations.....		2
Oöphorectomy associated with other operations.....		1
Condition found at operation:		Cases.
Jaundice.....		9
Stones in the gallbladder.....		46
Stones in the common duct.....		8
Regional lymphatics enlarged.....		6
Cholecystitis, Grade 1.....		0
Cholecystitis, Grade 2.....		32
Cholecystitis, Grade 3.....		12
Cholecystitis, Grade 4.....		4
Hepatitis, Grade 1.....		1
Hepatitis, Grade 2.....		0
Hepatitis, Grade 3.....		2
Hepatitis, Grade 4.....		0
Abscess of the liver.....		2
Pancreatitis, Grade 1.....		28
Pancreatitis, Grade 2.....		19
Pancreatitis, Grade 3.....		1
Pancreatitis, Grade 4.....		0
Data obtained from recent letters of inquiry:		
Cured (attacks of diarrhea in 3).....		30
Unimproved.....		2
No reply.....		16

TABLE 2

CHOLECYSTITIS WITH CIRRHOSIS

(Thirty-one Cases)

	Years
Average age of patients.....	46
Oldest.....	70
Youngest.....	29
Average duration of symptoms.....	6
Longest, twenty years; shortest (papilloma of gallbladder), one month.	
	Operations
Cholecystectomy.....	19
Choledochostomy.....	6
Gastro-enterostomy for duodenal ulcer associated with other operations, 1; excision of duodenal ulcer associated with other operations, 1.	
Cholecystostomy.....	6
Appendectomy associated with other operations.....	20
Condition found at operation:	Cases.
Jaundice.....	6
Stones in the gallbladder.....	12
Stones in the common duct.....	8
Cirrhosis, Grade 1.....	26
Cirrhosis, Grade 2.....	5
Cholecystitis, Grade 1.....	9
Cholecystitis, Grade 2.....	14
Cholecystitis, Grade 3.....	7
Cholecystitis, Grade 4.....	1
Pancreatitis, Grade 1.....	6
Pancreatitis, Grade 2.....	3
Pancreatitis, Grade 3.....	3
Enlargement of the regional lymphatics.....	6
Data obtained from recent letters of inquiry:	
Cured.....	17
Not improved.....	2
Not heard from.....	12

TABLE 3
CHOLECYSTITIS WITH ASSOCIATED HEPATITIS
(Forty-seven Cases)

	Years
Average age of patients.....	49
Oldest.....	69
Youngest.....	21
Average duration of symptoms.....	9
Longest, thirty-two years; shortest, three months.	
	Operations.
Cholecystectomy.....	41
Choledochotomy.....	6
Cholecystostomy.....	2
Appendectomy.....	25
Splenectomy associated with other operations.....	1
Condition found at operation:	Cases.
Jaundice.....	5
Stones in the gallbladder.....	22
Stones in the common duct.....	3
Regional lymphatics enlarged.....	7
Cholecystitis, Grade 1.....	14
Cholecystitis, Grade 2.....	22
Cholecystitis, Grade 3.....	6
Cholecystitis, Grade 4.....	5
Hepatitis, Grade 1 (local in 7).....	22
Hepatitis, Grade 2.....	12
Hepatitis, Grade 3.....	9
Hepatitis, Grade 4.....	4
Liver larger than normal.....	3
Pancreatitis, Grade 1.....	7
Pancreatitis, Grade 2.....	6
Pancreatitis, Grade 3.....	1
Present condition reported by letter satisfactory.....	24
Present condition the same or with recurrent attacks.....	4
Present condition not reported.....	19

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THE EFFECT OF TOTAL REMOVAL OF THE LIVER*

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In a previous article by one of us¹ a method was described for the total removal of the liver from the dog. The present report is a brief summary of the data obtained from a series of studies on the completely hepatectomized animal. Since it is our purpose to cover briefly the entire field investigated, review of the work on the subject by other observers as well as the details of our own methods of investigation are not given, but will be presented in future reports.

METHOD OF TOTAL REMOVAL OF THE LIVER

The liver is removed in three stages with a minimum interval of two weeks between operations. All operations are performed under ether anesthesia, and with aseptic surgical technic.

The first operation consists in making a reverse Eck fistula, that is, uniting, side to side, the portal vein and the vena cava and ligating the latter on the cephalic side of the stoma. At first a considerable portion of the blood from the lower extremities passes through the liver, but since the capillaries of the liver offer more resistance to the flow of blood than is necessary to develop a collateral circulation through the azygos and internal mammary veins, most of the blood soon passes by way of the latter channels.

The second operation consists in the ligation of the portal vein at its point of entrance into the liver. This causes all the blood from the viscera and hind limbs to return by way of the collateral vessels, the azygos, and the internal mammary veins.

At a third operation the entire liver is removed without in any way disturbing the general circulation.

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SYMPTOMS FOLLOWING TOTAL REMOVAL OF THE LIVER

The animal quickly recovers from the immediate effects of the operation and, for a period varying from two to ten hours, seems normal. It walks around, responds to call, drinks water or milk, and sometimes plays with other animals. Then a very characteristic sequence of events occurs. The first symptom noted is muscular weakness. This develops quickly, and in a short time the animal is unable to move any of its muscles except those of respiration. Coincident with this muscular weakness there is a loss of reflexes, after which the animal remains in a state of unconscious flaccidity. After a variable period, usually not more than one hour, there is a rather sudden return and exaggeration of the reflexes. Muscular twitchings develop which at first involve only separate muscles or small groups of muscles. Later, general convulsions occur, in one of which the animal dies.

The symptoms and the order of their occurrence are, therefore, muscular weakness, loss of reflexes, flaccidity, return and exaggeration of reflexes, muscular twitchings, convulsions, and death. The development of these symptoms is extraordinarily constant and varies but slightly in the different animals. The average animal, if untreated, dies within two hours after the first signs of muscular weakness have been noted.

THE RELATION OF BLOOD SUGAR TO THE DEVELOPMENT OF SYMPTOMS
FOLLOWING TOTAL REMOVAL OF THE LIVER

The most marked result following extirpation of the liver is a progressive fall of blood sugar. Coincident with this fall of blood sugar there is a decrease in the glycogen content of the muscles. The first symptoms noted after the removal of the liver occur concomitantly with this decrease in blood sugar. For instance, the animal appears perfectly normal in most cases until the blood sugar reaches from 0.06 to 0.05 per cent (estimation by the Benedict-Lewis method), when the first signs of muscular weakness are noted. By the time the animal is perfectly flaccid and unconscious, the blood sugar has dropped to 0.05 or 0.04 per cent, and at the time of death it is 0.04 or 0.03 per cent. We have never failed to note this direct relationship in decrease in blood sugar to the development of symptoms.

THE EFFECT OF THE ADMINISTRATION OF GLUCOSE AFTER REMOVAL OF
THE LIVER

If during any stage after development of symptoms to the point at which respiration has actually stopped, glucose is injected, the animal immediately and completely recovers. This recovery following the injection of glucose is a most remarkable phenomenon. An animal which is practically moribund and about to die is restored to a seemingly perfectly normal condition within one minute after the injection of 0.5 gm. of glucose per kilogram of body weight. We have noted instances in which an animal that was perfectly flaccid and unconscious was able to stand within thirty-five seconds after the glucose injection. The recovery is usually absolutely complete; the animal walks around, responds to call, and is seemingly normal in every respect.

The time the animal remains in this normal condition depends in general on the amount of glucose injected. One-fourth gram of glucose per kilogram of body weight will maintain the average animal for one hour. Then the blood sugar again decreases, the same set of symptoms develops, and the animal becomes moribund. Another injection of glucose again restores the animal to a normal condition. This process can be repeated many times.

After from twelve to eighteen hours, another set of symptoms develops and the animal may die with a blood sugar not below normal. If the glucose is administered orally, by rectum, or by continuous intravenous injection, the blood sugar may not decrease and the first set of symptoms does not develop. The oral administration seems best so far as keeping the animal alive for a long time is concerned. We have kept an animal alive, after total removal of the liver, for thirty-four hours. As the stomach may sometimes be traumatized during operation, we have found in some experiments that giving glucose through a jejunostomy, made at the time the liver is removed, is very satisfactory.

The only other substances thus far investigated that will produce this remarkable restoration to normal in the moribund animal following removal of the liver are maltose and mannose, and to a slight extent, galactose and dextrin. The beneficial action following the administration of the two latter substances is probably due to the presence of maltose or glucose as an adulterant. It should be recalled in this connection that all of these substances may be changed into glucose in the body, in which form they could be used.

In an attempt to find other substances besides glucose which would restore the animal to normal after the removal of the liver, and also to determine the manner in which glucose acts, the following substances were injected in amounts which seemed to correspond with the amount of glucose necessary to restore the moribund completely hepatectomized animal to normal.

Cane sugar, lactose, levulose, inulin, sodium chlorid, sodium sulphate, sodium carbonate, sodium bicarbonate, alcohol, glycerol, glycoll, lactic acid, acetic acid, hydrochloric acid, pyruvic acid, epinephrin, and pituitary extract. None of these had a restorative action.

CHARACTER OF SYMPTOMS THAT DEVELOP WITH A HIGH BLOOD SUGAR LEVEL AFTER THE ADMINISTRATION OF GLUCOSE

In the animals that have been kept alive for various periods by the administration of glucose, a group of symptoms develops entirely different from those associated with a decrease in blood sugar. All of these animals pass into coma and die quietly, usually without muscular twitchings. In many instances the coma is preceded by other symptoms not in any way similar to those due to lack of glucose. We have not determined the cause of this second group of symptoms which leads to death; it is still under investigation.

THE EFFECT OF THE REMOVAL OF THE LIVER PRECEDED BY THE REMOVAL OF THE PANCREAS

The blood sugar decreases seemingly more rapidly following the removal of the liver, if the pancreas has been removed from twenty-four to forty-eight hours before. The same group of symptoms develops as when only the liver is removed, but they usually occur at a higher blood sugar level in the absence of both glands. The injection of glucose after symptoms have developed will also restore the animal to normal, but the beneficial action is not long maintained and the animal dies in coma with a high blood sugar level.

If the pancreas has been removed more than from twenty-four to forty-eight hours previous to removal of the liver, the decrease of blood sugar following the removal of the latter organ still occurs, but the injection of glucose seems to produce little or no beneficial action and the animal dies in coma. Our data are as yet incomplete regarding this phase of the problem.

THE EFFECT OF REMOVAL OF THE LIVER ON THE BLOOD PRESSURE,
PULSE, RESPIRATION, AND TEMPERATURE

Following the removal of the liver, the blood pressure seems to be practically normal while the animal is active. When it first develops the symptoms associated with decreased blood sugar, the blood pressure is also decreased but is not necessarily very low. The injection of glucose restores the animal to consciousness without necessarily raising the blood pressure. The blood pressure gradually decreases, and after the necessary repeated injections of glucose a slight rise in blood pressure accompanies the injection.

The pulse is usually rapid, being practically twice the normal rate after the removal of the liver, and the injection of glucose produces a distinctly beneficial action on the heart.

The respiration undergoes certain changes following operation, varying with the condition of the animal. When it is in coma, the Cheyne-Stokes type of respiration is frequently noted.

The temperature usually continues normal until the animal becomes flacid. It is not unusual for the temperature to rise one degree higher than it was before the operation just previous to the development of muscular weakness.

THE EFFECT OF THE REMOVAL OF THE LIVER ON NITROGEN METABOLISM

If glucose is not given the completely hepatectomized animal, death usually occurs associated with low blood sugar before any pronounced change in nitrogen metabolism is noted. In animals treated with glucose, changes as follows occur:

1. The blood urea falls, sometimes being reduced more than 50 per cent.

2. The normal dog has no uric acid in his blood, but following the total removal of the liver there is a large amount, increasing with the length of time the animal lives.

3. The ammonia excretion in the urine is greatly increased, perhaps chiefly at the expense of urea, and the ratio may finally reach a level of 1:2. At this stage "rest nitrogen" increases rapidly in both blood and urine.

4. Creatin in the blood does not change following the extirpation of the liver.

5. Blood nonprotein nitrogen and blood amino-acid nitrogen

increase. Injection of glycocoll is followed by a rapid, almost quantitative increase in blood amino nitrogen, and after five hours both non-protein and amino-acid nitrogen are elevated to a point only slightly lower than maximum.

THE OCCURRENCE OF BILE PIGMENT IN THE URINE AND PLASMA AFTER THE REMOVAL OF THE LIVER

A few hours after complete hepatectomy the urine becomes colored and gives all the tests for bile pigment. The color of the urine and the reaction to the tests become progressively more pronounced the longer the animal lives.

The blood plasma, clear before operation, a few hours after operation develops a yellow tinge and many hours after the removal of the liver is quite yellow. The plasma also gives a positive test for bile pigment some time after operation. The fatty tissues of the completely hepatectomized animal also become yellow tinged, and an extract of them gives a positive test for bile pigment. There seems to be no doubt that bile pigment, or a substance responding to the tests for bile pigment, appears in the plasma, tissues, and urine after the removal of the liver.

THE EFFECT OF THE REMOVAL OF THE LIVER IN THE GOOSE

In the goose the portal vein normally may drain into the general venous system without passing through the liver, due to the presence of the circle of Jacobson. In this species, therefore, the liver can be removed in one operation.

The effects of extirpation of the liver in the goose differ slightly from those obtained in the dog. The symptoms are not so marked, the blood sugar does not decrease to such a low level, and the restoration after the injection of glucose is not so complete as in the dog. Uric acid, which is normally present in the blood of the goose, decreases and may disappear entirely. There is a very rapid rise in blood urea.

THE EFFECT OF REMOVAL OF THE PANCREAS AND THE LIVER IN THE GOOSE

If the pancreas is removed from the goose twenty-four hours before the removal of the liver, the blood sugar seems to drop even more

quickly. The animal becomes moribund after the removal of both glands, and is partially restored by the injection of glucose, but the beneficial action is not maintained for so long as when the liver alone is removed. We also have data which seem to show that if the pancreas is removed more than forty-eight hours before the liver is removed, the beneficial action of glucose is very slight.

THE EFFECT OF REMOVAL OF THE LIVER AND THE INJECTION OF GLUCOSE IN THE FROG

The liver can also be removed from the frog at one operation because the portal system normally sends some of its blood into the general systemic circulation without its passing through the liver. The blood sugar is very low in the normal animal of this species, and we have not been able to obtain enough blood to determine the level after the liver was removed.

The frog remains seemingly in a normal condition sometimes for as long as one week after hepatectomy. It then develops the same general condition that occurs in other species, and dies. The transition from a seemingly normal condition to a moribund condition is very rapid, taking place sometimes in less than one hour. The injection of glucose is but slightly beneficial.

VARIOUS DATA NOTED AFTER THE TOTAL REMOVAL OF THE LIVER

The character of the symptoms which develop after the total removal of the liver simulate quite closely those which are supposed to be associated with acidosis alkalosis. Therefore, it was anticipated that there might be one of these two conditions noted at the time the animal became moribund. However, it was found that the carbon dioxid combining power of the plasma and the hydrogen ion concentration of the blood varied but little in the specimens removed before operation from those removed at the time of death in the animals which were untreated with glucose. These slight variations were not great enough to account for any of the symptoms. Neither have we been able to obtain evidence that disturbance in the reaction of the blood in the animals that are kept alive for many hours after the removal of the liver, by the administration of glucose, is extensive enough to be a factor of consequence. At first there is a slight decrease in the coagulation time of the blood, occurring within a few hours after

operation. Later there is a gradual increase in the coagulation time, and in many of the animals that are kept alive for a considerable period by the administration of glucose an oozing hemorrhage occurred from all the abraded surfaces. We have not determined whether this is due to the lack of regeneration of fibrinogen.

THE REMOVAL OF THE LIVER FUNCTIONALLY BY CIRCULATORY EXCLUSION

In previous studies on the effect of the removal of the liver, except in those instances in which the investigator used a species having the circle of Jacobson, the organ has been removed by one of two methods. Some investigators performed an Eck fistula operation and later removed the liver lobe by lobe. Owing to the intimate relation of the vena cava and the liver, it is impossible to remove all the liver by this method without injuring the vena cava. In our experiments when this method was employed it was necessary to leave a minimum of 10 per cent of the total amount of liver tissue in order that the vena cava might be left intact. If this remaining liver tissue is removed, the vena cava is always injured and a circulatory disturbance produced, while if some liver tissue is left, it is without adequate blood supply, undergoes autolysis, and produces toxemia.

The other method of functional removal of the liver consists in performing an Eck fistula operation and then ligating the arterial blood vessels to the organ. This leaves the entire organ in the peritoneal cavity without a blood supply. This method also has two serious objections: (1) An enormous amount of liver tissue without blood supply is left in the peritoneal cavity where it undergoes autolysis, and the absorption of the broken down liver substance is a definite complicating factor, and (2) variations in the respiratory movements force blood back through the vena cava into the hepatic veins and thus wash out material in the liver.

We have studied the effect of removal of the liver by both of these methods, particularly the latter, in order to compare the results with those obtained by our own method of total removal, and these give us a basis for comparing our data with those previously reported. We find that an animal from which the liver has been removed functionally will have the same decrease in blood sugar that takes place when the organ is surgically extirpated. The animal develops symptoms at a much higher level of blood sugar when the organ is left in place without

its blood supply than when it is completely removed; and while glucose injection restores the animal with the functionally removed liver the first time it becomes moribund, a second injection rarely proves of any value, and the animal dies within a very few hours after the exclusion of the liver. Our data tend to show that this method of liver exclusion will assist in ascertaining a few facts concerning the physiology of the liver, but it is only possible to obtain clean-cut facts regarding the results of removal of the liver when complete hepatectomy is done.

THE EFFECT OF PARTIAL REMOVAL OF THE LIVER

All except the two lower right lobes of the liver of the dog can be removed without serious damage to the portal and vena cava circulation. By weighing the various lobes of many livers of this species we have estimated that approximately 70 per cent of the organ is thus removed. The animals from which such large amounts of liver have been taken do not seem to suffer from such loss. The reason for this is readily determined by examination a few months after operation, when it is noted that the two remaining lobes have enlarged until the amount of tissue is practically the same as before operation. Hepatic insufficiency cannot be produced by this method.

If an Eck fistula operation has been performed some time before the removal of the liver tissue, regeneration does not occur, or not to the extent it occurs if the portal circulation is intact. It seems that the loss of the portal circulation definitely prevents or decreases regeneration of the liver. In animals with Eck fistulas, therefore, it is possible to remove all the liver except the two lower right lobes and produce a definite chronic liver insufficiency. Our studies concerning this phase of the problem are very incomplete; but facts as follows have been determined.

Such animals recover from the immediate effects of the operation, and for the first few weeks little change is noted. Then they gradually lose weight, strength, and appetite and become emaciated, although no definite cause for this can be determined. Jaundice does not occur nor has any other specific change been noted.

INTRAVENOUS GLUCOSE TOLERANCE TESTS

The results of our investigation on the liver have led us deeply into the problem of glucose metabolism. In order to study some phases

of the subject, we have made hundreds of intravenous blood sugar tolerance tests in animals in various conditions. Many facts have been ascertained with regard to the relation of the liver and the pancreas to sugar metabolism, and with regard to the storage of sugar as glycogen in the liver and muscles. These data are too voluminous for this paper, but will be presented later.

SUMMARY

It is not safe to draw definite conclusions at this time from the results of the studies on a problem so fundamental. However, it seems evident that the liver is vitally concerned with the maintenance of a proper blood sugar level which is necessary for life. If this level is maintained artificially after the removal of the liver, life is greatly prolonged and subsequent death is not due to lack of blood sugar, but to some as yet unknown factor. It does not seem to be due to (1) acidosis or alkalosis; (2) changes in nitrogen metabolism which are usually considered in connection with the liver function; (3) blood destruction; (4) changes in blood volume; (5) direct changes in blood pressure, respiration, temperature or cardiac function, or (6) variation in pathologic environment of the cell in relation to the body fluids.

Besides the function of maintaining a proper blood sugar level, the liver is probably of great importance in the formation of blood urea, purin metabolism, ammonia balance, amino-acid metabolism, formation of fibrinogen, the removal from the blood stream of the derivatives of broken down blood, and in protecting the body against substances absorbed through the gastro-intestinal tract, but not made innocuous by the gastro-intestinal wall. The pancreas and the liver have a reciprocal relation to the blood sugar.

The authors have made these studies in collaboration with Carl S. Williamson, Frank J. Heck, and Edna V. Schmidt.

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THE SURGICAL SIGNIFICANCE OF HEPATIC INCOMPETENCY*

WILLIAM J. MAYO

The Great War brought to a close a period in scientific surgery of which Dr. John B. Murphy was the most brilliant exponent. This period was characterized by the advancement of the principles of surgery, investigation of the relation of microorganisms to disease, and the development of clinical medicine on a pathologic basis. Animal experimentation and the test tube marched side by side with clinical surgery and illumined many dark pages in our understanding of the phenomena of disease. The development of clinical surgery during the last generation was essentially regional, and in this development no one played so great a part as the distinguished man in whose honor this annual address is given.

Briefly to call attention to just what Murphy accomplished and the breadth and scope of his genius, we may cite his contributions to abdominal surgery for which he first became known. The Haymarket riots brought his name into prominence. While Bull preceded Murphy in the successful repair of gunshot wounds of the intestine, the brilliance of Murphy's performance gave vitality to Bull's exploit, and Murphy followed his operative work by promulgating the surgical principles governing gunshot wounds of the abdomen which guide us today. Murphy's early grasp of the appendicitis problem was equally firm and sure. His paper "Ileus," published in 1896, is one of the most valuable contributions to American surgery, and even today we fail to realize the importance of the parallel artery of the small intestine without corresponding veins which Murphy pointed out as a frequent cause of gangrene of the obstructed intestinal wall. We speak of "cutting off" the circulation in any part of the body, when we usually mean the opposite. When the arterial circulation is cut off "white death" follows, a rare form of necrosis. "Black death" is the usual condition,

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the arteries continuing to carry blood into the involved gut, the obstructed venous flow choking the doomed area. Murphy made valuable contributions also to the study of tuberculosis of the peritoneum, pointing out that it is secondary to a local focus, and his genius was particularly manifest in clearing up moot points in the surgery of the biliary tract.

Murphy's mind, while never abandoning an accepted field of research, ever turned to new and unexplored regions of the body. His oration on "Thoracic surgery," before the American Medical Association in 1898, brought out work of a fundamental character, showing the effect of the size of external pleural openings on collapse of the lungs, and that the diaphragm is essentially the piston of a thoracic pump. In surgery of the nervous system his contributions were equally important, stressing the fact that peripheral nerves divided proximal to the ganglion never regenerate and that a complete severance of the spinal cord due to injury is irreparable. In surgery of the vascular system, also, he dealt with fundamental problems and successfully sutured large vessels; his work in this field has been the basis of productive research. The more recent contributions which were made by him during the years immediately preceding his too early demise were in surgery of the bones and joints, where he greatly assisted orthopedic surgery to free itself from the shackles of the harness maker.

Other surgeons of Murphy's day and generation may be compared with him in various limited fields of surgical endeavor, but we must remember the number of targets into which he shot and that he always rang the bell.

Murphy was a voluminous writer and greatly enriched surgical literature. By these printed pages posterity will know him, but to those of us who have been inspired by his magnetic personality and who have, with rapt interest, followed his clinical teachings, visible evidences of the printed page are but the ghost hovering over the grave of the greatest surgeon of the last generation.

I knew Murphy well; his was not the nature that desired praise, but with the divine spark he desired ever to kindle new fires under old misconceptions. Therefore, in our annual memorial tribute to Murphy we should strive to emulate his standards and devote our endeavors to the advancement of the science of surgery, even as he devoted his life to this cause.

As the result of many causes, of which the profound influence of

the war may be counted as one, we see, perhaps dimly, that surgery is taking on a new aspect. It is no longer possible for the individual surgeon, in the face of the enormous amount of new and, as yet, unorganized knowledge, to cover the ground that Murphy covered.

Our day of higher specialization and the correlation of the work of specialists in many fields is the foundation on which future progress depends. We see this exemplified in the study of shock in its relation to the nervous system as influencing operation, in the closer study of the heart, and the effect that changes in the vascular system may have on surgical conditions. We are beginning to recognize that although respiratory failure is the most frequent immediate cause of the termination of life, the material causes which produce the terminal pulmonary catastrophe is usually brought to the lungs through the blood stream, seldom by way of the respiratory passages, and that the influence of the anesthetic is slight in producing postoperative pulmonary complications after surgical operations, which are equally frequent after local anesthetic, nitrous oxid and oxygen, and ether. We are also gaining knowledge of the relation of incompetence of the kidney to the cause of death. We have found that the kidneys do not secrete urine, but filter urine, and that with the urine are eliminated body waste and toxic products strained from the general circulation, that the kidneys are not often the primary cause of death, kidney failure being due to overload, and the development of acute conditions on preëxisting lesions. Studies of the blood have, therefore, become of the utmost importance because we recognize as never before that the toxic material which produces these wide-spread manifestations may affect more specifically certain of the vital organs. As shown by Rosenow, the bacteria and other toxic bodies are carried through the blood stream to the organs which they damage and lead to surgical complications and often to death. From this engrossing study has developed the modern doctrine of focal infections which is attracting the attention of present-day investigators. The study of the methods by which purification of the blood is effected presents a promising field for investigation.

The paramount importance of the hepatic function: The liver was recognized, even by the ancients, as the king of organs, standing as a buffer, on the one hand, between the general circulatory system and the gastro-intestinal tract, and, on the other hand, between the general circulation and the spleen, which filters from the blood microorganisms and toxins that it is unable to destroy, sending them to the liver through

the portal circulation for destruction and detoxication. The liver detoxicates chemical poisons, such as chloroform, phosphorus, and arsenic, as well as biochemical poisons produced in the body. Yet, for many reasons, we know little concerning the functions or early pathologic conditions of the liver. Its concealed situation prevents us from accurate means from without of early diagnosis. Its power to regenerate injured cells and form new cells is not equalled by any other organ of the body, and its enormous margin of safety prevents us from knowing just what is taking place in the earlier stages of hepatic disease, and the appalling nature of the pathologic changes, when they are sufficient to enable physical demonstration, has made the liver an organ of mystery and conjecture. I venture to predict that the next few years will bring forth productive research demonstrating that the causes of many of the changes in the so-called vital organs which lead to death do not primarily originate in the nervous system, heart, lungs, or kidneys, but are the results of hepatic insufficiency, leading to insufficient purification of the blood, thus making possible much sound prophylaxis.

I have, on a previous occasion, discussed the function and pathology of the liver in relation to the hepatic cell. All the liver cells are alike. Therefore, the pathologic architecture in hepatic disease is simple. If the pathologic process in the hepatic cell is acute, the destructive process assumes the nature of fatty metamorphosis. If the process is chronic, the destroyed cells are replaced by connective tissue, producing cirrhosis. If the cause of the hepatic cirrhosis is carried to the liver by the portal circulation, the new connective-tissue deposit is around the portal vessels, obstructing the delivery of the blood from the portal circulation to the hepatic cells, and the patient does not die from hepatic insufficiency, but from circulatory disturbances which lead to ascites and gastro-intestinal hemorrhages caused by the portal cirrhosis. On the contrary, in biliary cirrhosis the causes of the injury to the hepatic cell are brought by the biliary channels, and the connective-tissue deposits are around the bile ducts, resulting in obstructions to the flow of bile, so that death occurs from cholemia in cases of biliary cirrhosis.

In connection with hepatic cirrhosis passing attention should be given to the work of Herrick, who shows the effect of the hepatic artery on the cirrhotic process. The pressure in the portal vein is 30 mm. and the pressure in the artery 130 mm. The greater the obstruction to the portal circulation, the greater the circulatory embarrass-

ment occasioned by the arterial counterpressure. The slight amount of oxygen needed by the hepatic cell for its own purposes is furnished by the hepatic artery. It is interesting to note, in connection with carbohydrate metabolism, that in the liver of carnivorous animals the ligation of the hepatic artery may not cause serious effects, while in the herbivorous, it usually causes death.

The liver acts on nonoxygenized blood: The hepatic cell has an unrivalled capacity to act on portal blood, which has already lost its oxygen. The blood on which the liver acts is venous and leaves the liver as venous blood through the hepatic veins; oxygen plays little if any part in the changes which take place. Physiologists point out that the hepatic artery furnishes oxygen to the liver, and this would appear to be true so far as the liver tissue is concerned, but the supply is not sufficient to lead us to believe that oxygen is necessary to its function. Compare the arterial blood supply of the liver, weighing 50 to 55 ounces, with the huge arterial blood supply of the spleen and kidney, each of which weighs only a few ounces, but uses a great amount of oxygen in functioning. The hepatic artery is not large and its content is reduced greatly by giving off the gastroduodenal artery, the superior pyloric artery, the supraduodenal branches, and the cystic artery; thus two-thirds of its volume is gone before it reaches the liver. Possibly one of the functions of the spleen is the removal of oxygen from the blood which enters the liver by this route. The functions of the liver are: (1) defense against invasion of the body by microorganisms and the detoxication of toxic products brought to the liver from the portal circulation, (2) fat metabolism, (3) protein metabolism, (4) carbohydrate metabolism, and (5) bile function.

I cannot discuss here the fascinating problem of the effect of the liver on bacteria and toxic products of a chemic and biochemic nature. With regard to the effect of the liver on the final conversion of proteins into consumable material, I would point out that the amino-acids in the body are developed in the liver from protein metabolism begun in the intestinal tract. It may also be stated that the liver is one of the great storehouses for fat, and the convertor of fat into consumable material for the use of the body. Urea is the ash of protein burning, and certain higher fatty acids, which may be a residue of improperly oxydized fats in combination with ash of improper protein burning, are back of many of the circulatory and vascular changes which lead to insufficiency of the vital organs, especially of the kidneys.

Sugar-forming function of the liver: I regret that many aspects of these various problems, although germane to this discussion, must be omitted for lack of time. I shall concentrate attention on the relation of carbohydrate metabolism and bile function, the liver, and on the organism as a whole. The end stages of carbohydrate metabolism take place in the liver and the distribution of sugar for the heat and energy of the body takes place through the blood stream. The ash of sugar oxidation in the tissues is passed out of the body through the lungs as carbon dioxide. Normally, considerable amounts of glycogen are stored in the liver and this store under great stress is fed more liberally into the blood stream, and in conjunction with the internal secretions gives the utmost obtainable energy under the influence of anger or fear, acting through the autonomic nervous system. In starvation the stored-up glycogen is exhausted and the alkalinity of the blood reduced, so-called acidosis. The pernicious vomiting of pregnancy is believed by Harding to be due to the exhaustion of the stored liver glycogen by the constitutional necessities of the mother and child; the treatment of pernicious vomiting of pregnancy by carbohydrate feeding appears to bear out this theory. As a rule reduction of sugar below normal is accompanied by dehydration. In the estimation of the blood sugar, which may appear to be normal because of the increased blood viscosity, allowance must be made for sufficient fluids to approximate normal conditions.

The ash of carbohydrate oxidation is much less poisonous than the ash of protein and fat combustion to which diabetic coma is due. As shown by Woodyatt, the proper burning of protein and the higher fatty acids is not complete unless a percentage of carbohydrates is burned in conjunction; hence the value of starvation in the management of diabetes, by reducing fats and proteins as well as carbohydrates, over the old treatment by carbohydrate deprivation alone. Chronic bodily exhaustion is associated with disturbed function of the liver and usually with diminution of sugar metabolism. Mann has shown that if the liver of an animal is removed, death results in from five to twelve hours, but if the blood sugar is maintained the animal will live for from twenty-four to thirty-five hours, and even when apparently moribund can be resuscitated by intravenous injections of glucose.

Function of the bile: The hepatic lobule has for its center a bile channel. The venous blood from the portal circulation is acted on by the hepatic cell and passes away in the venous plexus of the collecting

hepatic veins; the refuse, if it may be so-called, takes its way to the intestinal tract in the form of bile. Nature is most economical in her operations. The bile in the intestinal tract has valuable direct and indirect functions, aiding in pancreatic and intestinal digestion. The fluids and certain constituents, such as the lipoids, are reabsorbed in the intestinal tract, while the bile pigments which contain the more active poisons of the biliary content pass and are excreted. When the bile is obstructed in its passage into the intestinal tract it is absorbed in the blood, the biliary pigments unite with the calcium in the blood, and, in the course of time, three weeks or more, a calcium exhaustion may occur. The reduction of the calcium reserve in the blood lengthens the coagulation time. The bile pigments, to which much of the ill effects of cholemia are due, are excreted from the blood by the kidneys. The cholemia not only affects the liver, but the tissues of the body as a whole. Cholemia brings about a pernicious dehydration, interferes with the action of the liver, especially in its sugar-forming function, and exhausts the hepatic sugar reserve. The secondary effects of cholemia are felt by every organ of the body, especially by the kidneys, which are called on to excrete a great amount of bile pigments and other products of disturbed metabolism which may result in kidney incompetency as well as liver insufficiency. In many respects the urine function of the kidney and the bile function of the liver are comparable. Especially is this true under stress. There is a close connection with diseases of the skin, liver, and kidneys, as though there were a correlation of function, notably the production of acute nephritis in the exanthemas and the poisonous bile of extensive burns of the skin which results in fatal duodenal ulceration.

OVERCOMING THE EVILS OF CHOLEMIA

The practical questions connected with cholemia in its relation to surgery are obvious, and the successful solution of these problems carries lessons which can be applied to various other forms of hepatic incompetence. Bell and Walters, of the Clinic, have investigated cases of chronic jaundice in which operation had been performed for any and all conditions and death followed. Fifty-three per cent of these patients had blood in the peritoneal cavity, although not necessarily enough to account for the death. In comparable cases in which no jaundice was present there was only one instance of intraperitoneal hemorrhage,

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which was caused by the slipping of a ligature on the cystic artery. In the jaundiced patients the blood in the peritoneal cavity was from capillary hemorrhage; in no instance was the bleeding from demonstrable vessels.

Wright has pointed out that the loss of normal coagulation of the blood is due to calcium exhaustion and that the calcium can be restored by giving chlorid of calcium by way of the gastro-intestinal tract. Lee and Vincent have shown that the amount of calcium that can be taken up from the gastro-intestinal tract is relatively small, but it may readily be given in the form of chlorid of calcium intravenously, in which form it affects the blood coagulation in a short time. Walters has been able to show that the coagulation time can be restored in from two to six hours after the intravenous injection of chlorid of calcium, and that the procedure is harmless. He repeated the experiments of other observers, and it was not only shown that the administration of calcium promptly restored the blood coagulability due to calcium exhaustion, but that the coagulability of normal blood could be hastened in this manner.

In the cholemic state, however, calcium may not be the only factor in the tendency to bleed, and when the calcium exhaustion has been remedied, if the coagulation time is still high, transfusion of blood is indicated. Two other factors of importance must be considered in counteracting the evil effects of the cholemic state; first, to restore the normal amount of blood sugar and the liver glycogen reserve, and second, to overcome the dehydration, and thus aid the kidney in the elimination of bile pigments, which are the chief causes of the general exhaustion of the cholemic patient. Fortunately this can be accomplished by increasing the quantity of ingested carbohydrate and fluid intake by mouth, by the Murphy drip, or if necessary, by subcutaneous infusions of from 3 to 5 per cent solution of glucose which can be introduced subcutaneously up to 2,000 to 3,000 c.c. in twenty-four hours. The surgical indications are most safely met by great care and gentleness in handling the tissues of cholemic patients during operation. No operative procedure which is not essential to the immediate recovery of the patient should be undertaken in the presence of intense jaundice. For example, after removing stones from the common duct in the cholemic patient cholecystectomy is seldom advisable.

By following these principles we have been able safely to operate on twenty successive patients with obstructive jaundice, many of whom,

because of subcutaneous hemorrhages and general exhaustion, formerly would have been considered beyond surgical relief.

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POSTOPERATIVE PERITONEAL ADHESIONS: AN EXPERIMENTAL STUDY*

CARL S. WILLIAMSON AND FRANK C. MANN

During the last five years we have made cursory observations on the formation of postoperative peritoneal adhesions following various operations within the abdominal cavity, and have tried out most of the procedures recommended for the prevention of adhesions. It is our purpose here briefly to give the results of these experiments.

The methods employed to prevent peritoneal adhesions may be divided into three groups: (1) prophylaxis, (2) foreign substances for the purpose of keeping the injured surface from contact with any other surface of the peritoneum, and (3) the retardation or inhibition of some element in the process of healing.

There is no doubt that the employment of prophylaxis, as emphasized by so many investigators of this subject, is the most important means at the surgeon's command of preventing adhesions. Whatever decrease there has been in postoperative adhesions can be attributed mainly to the development of better technic in which abuse of the peritoneum was obviated as much as is compatible with proper surgical procedure. The formation of peritoneal adhesions is a part of the process of healing, and in this respect should be properly guided by the surgeon and not necessarily prevented. In many operations the formation of a certain amount of adhesions is desirable. In other operations, either because of absolutely necessary operative trauma or resulting pathologic conditions, raw peritoneal surfaces are unavoidable and impossible to repair. Adhesions form on this base, and remedial measures only make the condition worse. A method which would prevent the formation of adhesions and yet allow normal healing would be of inestimable value in such cases. It was with the hope of discovery of such a method that our researches were conducted.

In attempting to prevent peritoneal adhesions innumerable methods and substances have been recommended, for example: The stimulation

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of active peristalsis by purgation; the change in the posture of the patient; various oils intraperitoneally, such as liquid vaselin and olive oil; fluid, such as normal salt solution; nonabsorbable membranes, such as rubber dam, oiled silk, silver foil, tin foil, and collodion; absorbable membrane, such as catgut, cargile membrane, amniotic membrane, and fish bladder; viscid substances, such as glucose, dextrin, and gum acacia; various irritants, such as iodine and ether; and substances which will prevent the process of healing, such as sodium citrate and fibrolysin.

In attempting to determine whether any of the various methods or substances recommended are of value in the prevention of adhesions it is necessary carefully to standardize the method of operation. We found this rather difficult since the reaction of the peritoneum varies quite markedly in individuals. There is also a great variation in species. The formation of adhesions in the rabbit is somewhat different from the same process in dog and in man. While we employed various species of animals, particularly the dog and the rabbit, we were convinced that conclusions applicable to man could only be drawn from the experiments performed on the dog. We also found it difficult to standardize a procedure involving the gastro-intestinal tract because of the wide individual variation in the formation of adhesions following trauma to this structure. After a number of observations we found a technic which suited our purpose admirably.

TECHNIC

The operative procedures were carried out under surgical anesthesia and sterile technic. The liver was exposed and areas on each of the upper and lower surfaces were traumatized gently with dry gauze until bleeding occurred. We found that after such trauma on a dog's liver a few adhesions between the traumatized surface and the parietal peritoneum on the upper side and the adjacent abdominal organs on the lower side always occurred. The material to be tested was placed over one of the traumatized surfaces of the liver. If the material was of any value the result of preventing adhesions to the traumatized area was quite definite. The other traumatized surface of the liver was kept as a control, and it should be noted that adhesions never failed to occur. This gave us a procedure as nearly standard as could be hoped for.

After carrying out the foregoing procedure the abdomen was closed

and after a definite length of time, at another laparotomy, the formation of adhesions on the two surfaces of the liver was noted. In a few instances in which the material to be tested was not adaptable to this technic, various intestinal operations were performed and the material used over the line of suture. The latter experiments serve to emphasize the fact that the reaction of the peritoneum varies considerably in individuals.

RESULTS

Practically all the substances used to prevent peritoneal adhesions by keeping the injured surface from contact with other surfaces until healing takes place, can be included in three groups: (1) fluids, (2) substances which are absorbed, and (3) substances which are organized. We soon found that each group had some unsatisfactory elements. Fluids, such as sodium chlorid, are hard to apply because they do not remain at the site of trauma, but gravitate to other portions of the abdominal cavity, depending on the position of the body. Substances that are absorbed, such as cargile membrane, may produce more reaction in the process of their absorption than the original trauma. Substances necessitating organization, such as rubber tissue and oiled silk, have the disadvantage of having to be removed subsequently.

Many of the procedures that have been recommended to prevent adhesions in man are not adaptable to standard laboratory conditions; we have, therefore, omitted some of them from our review. The list of substances actually employed under the standardized conditions as described includes paraffin oil, olive oil, lanolin, boric acid and lanolin, sodium chlorid, iodine, ether, glucose, dextrin, silver foil, cargile membrane, catgut, and rubber dam. Our results in the employment of all these substances may be summarized by stating that our experiments did not develop anything of value in the prevention of adhesions. In many instances the substances were decidedly harmful.

As we have stated, the formation of peritoneal adhesions is a part of the process of healing, and it is questionable if it is ever advisable to interfere with the normal process. Sodium citrate is supposed to prevent the formation of adhesion by preventing the formation of fibrin and, thus, the process of healing. In our experiments it not only failed to prevent the formation of adhesions, but in some instances it seemed harmful, since the oozing of blood from the traumatized surface was prolonged.

After a careful consideration of the substances employed to prevent adhesions, it seemed to us that the value of such a substance would be enhanced if, besides its usual attributes, it should liquidize slowly. The ideal substance to fulfil such requirements should have adhesive qualities that would enable it to adhere to the site of the traumatized area, thus keeping other surfaces from contact. The substance should dissolve slowly at body temperature and be absorbed from the general peritoneal cavity. The rate of dissolution should be such that the substance will protect the traumatized surface for several hours. It is almost needless to add that the substance should have many other characteristics, such as the possibility of sterilization, inert as regards healing, and the reaction of the peritoneum.

After experimenting with many substances, a mixture of gelatin and gum acacia seemed to furnish the desired characteristics. Both of these substances have been employed previously for this purpose. Gelatin seems to have been discarded because it irritated the peritoneum; acacia seemed to produce good experimental results, but was never given an extensive trial; the substances used separately have the serious objection of not adhering closely.

The gelatin and gum acacia were made into a solution in the ratio of 25 per cent of each to 50 per cent of water and produced a substance which differs in some respects from either of the mother ingredients. It has extraordinary adhesive qualities; so much so that at body temperature it will stick to practically everything, including the peritoneal surface. At room temperature it forms a tough membrane not unlike rubber. It is easily sterilized by boiling, but does not remain the same after sterilization in the autoclave. At body temperature it is a semi-solid. The gelatin acacia mixture, placed in the peritoneal cavity, sticks to the site of application, causes absolutely no reaction, dissolves slowly within from four to eight hours, and is absorbed from the general body cavity.

THE METHOD OF PREPARING AND APPLYING THE GUM-ACACIA-GELATIN MIXTURE

The acacia should be obtained in lumps instead of in powder since the powdered preparation is not of a very good quality. It is powdered in a mortar and then dissolved in normal saline solution. An equal amount of gelatin is added and when both substances are thoroughly

dissolved the mixture is filtered through three or four thicknesses of gauze. The filtrate is then heated on the water bath until it is concentrated to the point at which the fluid content equals about 50 per cent of the mixture. While still quite hot the solution is poured into lead tubes of the type employed for tooth paste. After the tube is filled the open end is closed by folding until it is tight. The tubes are placed upright in a container with the screw-end down and boiled in water for from twenty to thirty minutes. They are then removed from the water and dropped in a jar of 70 per cent alcohol which is kept tightly closed.

When applied at operation the folded end of the tube is grasped with a sterile hemostat, held in hot water for a minute or two to liquefy the mixture, and then expressed at the desired site of application by simply unscrewing the top and rolling the closed end over the hemostat. Care must be taken to keep the material from anything except the desired site, since its extreme adhesive qualities make it very difficult to handle.

SUMMARY

We have used the material in a large series of experiments and the results, on the whole, have been satisfactory. The traumatized surface of the liver heals well under the layer of solution. It would seem, therefore, that it has prevented adhesions, but bearing in mind the marked individual variation in the quantity of adhesions that may develop, we hesitate unqualifiedly to state that it is of much practical value in their prevention. Furthermore, we have not as yet worked out a complete satisfactory method of making and applying the mixture, so we do not recommend it to be entirely safe from the dangers of infection. We can, however, state definitely that of all the materials thus far advocated, that we have been able to investigate experimentally, the gum-acacia-gelatin mixture offers the best chance for development. Our investigation of the various substances recommended for the prevention of peritoneal adhesions convinces us that surgeons are not justified in using them in the abdominal cavity.

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DIVERTICULITIS OF THE LARGE BOWEL*

JAMES C. MASSON

Diverticulitis was not recognized as a surgical entity until 1898. In that year Graser demonstrated the presence of an inflamed diverticulum of the large bowel as the cause of a left-sided peritonitis. Previous to that time the gross lesions produced by the inflamed process with or without malignant change had often been found at operation and at necropsy, but their etiology had not been understood and many of the inflamed masses were regarded as malignant. One of the earliest articles which no doubt referred to the condition was published by Virchow, in 1853, under the title of "Isolated circumscribed adhesive peritonitis of the colon." Following the publication of Graser's paper many surgeons from different countries reported cases. One of the first articles in the English language was published in 1904 by Beer; he referred mostly to the work done in Germany. In 1907, Mayo, Wilson, and Giffin reported in detail, with pathologic findings, five cases in which the colon had been resected for diverticulitis, and referred to several other cases in which operation had been performed in the Clinic in which there was little doubt that diverticulitis existed. Three of the operations were performed for vesicosigmoidal fistula of inflammatory origin. In 1904, Moynihan read a paper before the Clinical Society of London entitled "The mimicry of malignant disease of the large intestine," which referred to diverticulitis. Few cases were reported before 1914, and they were all diagnosed on the operating table or at necropsy. In that year Carman reported three cases. In the first case he had not been able to account for several small barium shadows outside the lumen of the bowel. From the similarity of the history in this case to the histories in the cases of diverticulitis which had been found at operation W. J. Mayo suggested the possibility of multiple diverticula of the large bowel, and exploration confirmed the diagnosis. Since that time numerous cases have been recognized

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clinically. In many cases the symptoms are so mild that surgery is not indicated. During the last eighteen years 289 cases have been diagnosed diverticulitis; operation has been performed in only 116.

Diverticula may be found throughout the entire length of the intestinal tract. Hansemann reported a case examined at necropsy with more than 400 sacculations, no doubt congenital. I shall discuss here, however, only the "acquired" or "false" diverticula found in the

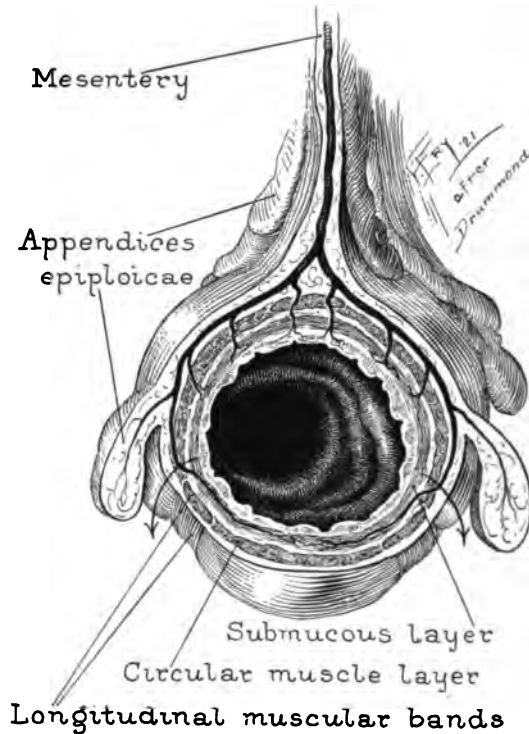


FIG. 73.—Distribution of the vessels of the pelvic colon. Arrows indicate the probable sites of diverticula.

large bowel, especially in the sigmoid and descending colon. They may be found at any point on the circumference of the bowel, but the greater number are on the sides between the lateral and mesocolic bands. Figure 73 shows the anatomy of the bowel wall with the weak points on the side of the viscus where the blood vessels pierce the circular muscle. The diverticula have been aptly called "mucosal herniæ" by McGrath. Small projections of mucous membrane first penetrate the muscular

wall and then become covered with subserous fat and peritoneum. They vary in shape and size; some are straight and others flask shaped. As they grow they follow the path of least resistance, which is toward the mesentery or into the appendices epiploicæ. In some cases they are mere recesses of mucous membrane in the muscular wall; in other cases they contain fecaliths 4 by 5 cm. in diameter (Fig. 74).

I have recently reviewed the histories of the 116 patients operated on for diverticulitis in the Mayo Clinic since 1902. Eighty-one of the

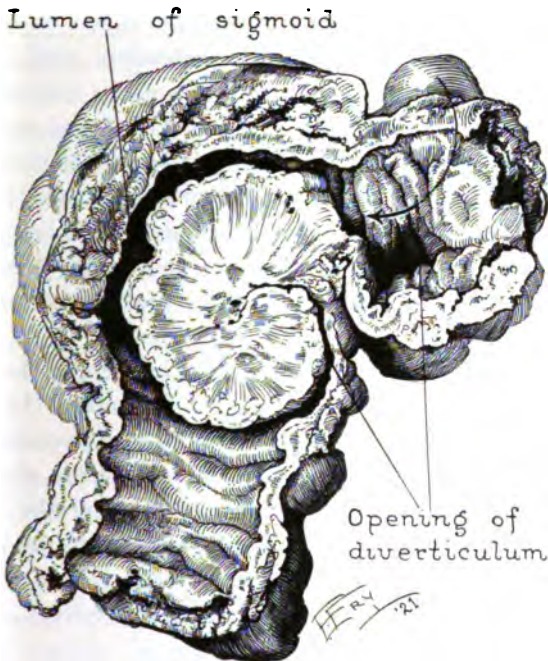


FIG. 74 (Case A84962).—Diverticulitis of the sigmoid. Inflammatory mass causing obstruction.

patients were males and thirty-five were females. The youngest patient was fifteen years of age and the oldest seventy-five years. Several authors, including Erdman, have reported diverticulitis in children, but it is essentially a disease of middle life and old age. The average age of our patients was fifty-two years. Overweight has been considered a strong predisposing factor. The heaviest patient in our series weighed 230 pounds, the lightest, 109 pounds. The average weight was 170 pounds.

The cause of this condition is not well understood, but constipation or an increase in the pressure within the lumen of the colon is, without doubt, the most important consideration. Fifty-nine and forty-eight-hundredths per cent of our patients gave a history of obstinate constipation. Frequent straining at stool doubtless accounts for many cases in which constipation is not marked. An almost constant finding at operation or necropsy is an abnormal amount of fat in the wall of the bowel, in the appendices epiploicæ, and in the mesentery; this probably weakens the normal resistance of the wall of the viscus.

The physiologic rôle which the sigmoid is called on to perform in civilized countries results in frequent distention, with more or less solid fecal matter and gas. The use of copious enemas frequently adds to the dilatation. Venous congestion is a natural result of dilatation; this causes enlargement of the openings through the muscular part of the wall, resulting in points of lowered resistance through which mucosal hernias are liable to push. In some cases there probably is a congenital predisposition which results in poor muscular development. In other cases there is a tendency to fatty degeneration in the muscle after middle life.

Diverticulitis of the bowel is of special importance because it is a strong predisposing factor to malignancy. Seventeen (14.65 per cent) in our series had malignant changes at the time of operation. In some cases the malignancy, no doubt, starts in one of the diverticula as a result of chronic irritation of the mucous lining of the sacculæ by a fecalith, in other cases with stricture of the lumen of the bowel, as the result of kinking or pressure on the bowel from an inflammatory mass, since the mucosa is irritated by the passage of the fecal content under abnormal pressure at this point.

SYMPTOMATOLOGY

Uncomplicated diverticula of the large bowel give no signs on which a diagnosis can be made; nevertheless we must consider each one a source of possible general infection, peritonitis, or malignancy, since generally fecal matter is retained within the diverticulum which irritates the mucous lining and leads to ulceration. Ulceration permits the passage of bacteria or their toxins through the thinned-out wall and also predisposes to malignancy. Various authors have suggested the percentage of cases that give trouble, but this is a very

difficult question to settle. Probably many persons who die of old age without symptoms have multiple diverticula.

The outstanding symptom is constipation of long standing in patients past middle life who are somewhat overweight. Most patients have attacks of more or less severe pain. This was noted in 79.3 per cent of our cases. Each diverticulum is capable of producing the same condition clinically which acute, subacute, and chronic attacks of appendicitis may cause, such as general peritonitis, local peritonitis, localized abscess, obstruction of the bowel by adhesions or kinking, and fistulas into other organs. Sometimes a hyperplastic extramucosal inflammation produces a tumor which can be palpated for a few days, and then disappears to reappear again with another attack of pain, tenderness, and rigidity. This history was obtained in forty, about 94 per cent, of cases in which operation had been performed.

As a rule, the disease is limited to the sigmoid and descending colon, but it may be found throughout the entire length of the large bowel. In the ascending and transverse colon, however, where the fecal matter is more fluid, it seldom gives rise to trouble. Table 1 shows the location of the disease in the cases on which this report is based.

DIAGNOSIS

Diagnosis can be made only after careful consideration of all the facts. The conditions which have to be ruled out are malignancy, sigmoiditis, hyperplastic tuberculosis, actinomycosis, syphilis, lesions in the pelvis, and appendicitis. All patients in whom diverticulitis is suspected should be examined by a competent roentgenologist. The extraluminal shadows in the roentgenograms are proof of the condition, but when obstruction is present the filling defect is identical with that of malignancy. During an acute attack of peridiverticulitis of the sigmoid or descending colon the symptoms are the same as those of acute appendicitis, consequently the possibility of a left-sided appendix, or, if the patient is a woman, some inflammatory condition of the left tube or ovary, is to be considered. In such cases it is not advisable to make a roentgenogram; an exploratory operation is indicated. If the seat of trouble is in the rectum, or the transverse or ascending colon, the difficulty of diagnosis is increased. If peridiverticulitis is extensive, a mass may be felt during an attack; the mass gradually disappears after acute symptoms subside. In other cases the mass



FIG. 75 (Case A306103).—Roentgenogram of barium-filled colon, showing multiple diverticula distributed throughout its entire length.



FIG. 76 (Case A105595).—Roentgenogram of barium-filled colon with diverticula of the sigmoid and an occasional small diverticulum of the descending colon.

suddenly disappears as the result of spontaneous rupture of an abscess into some hollow viscus, most commonly the urinary bladder or some part of the large bowel (Figs. 75 and 76).

As the condition is extramucosal, macroscopic blood is seldom found in the stool, while in cancer it is almost a constant finding. Since the openings in the lumen of the bowel are very small and can seldom be seen the sigmoidoscope is of little or no aid in the diagnosis. Negative findings rule out malignancy. Furthermore, diverticulitis does not produce emaciation, anemia, or cachexia, even when there is marked stenosis. Diverticulitis and carcinoma are frequently found coexisting in the same section of bowel. In the majority of cases the malignant condition is no doubt secondary and is the result of chronic ulceration and interference with circulation. On the other hand, in cases of carcinoma with partial obstruction from a napkin-ring type of growth of long standing with marked dilatation of the bowel above the growth, it is possible that the diverticula may have developed later.

TREATMENT

Some authors, among whom are Telling and Erdman, advise operation in all cases in which the condition is recognized. This is a most radical opinion, I believe, since the operation, with the best technic, is performed with considerable risk. As Turner expressed it, "Our difficulty will commence when the condition is better understood. It is all very well to say that surgery is the only remedy, but it is a formidable undertaking to excise a colon simply because it harbors multiple diverticula which have not caused serious symptoms." Operations for diverticulitis probably carry the same mortality as operations for malignancy, approximately 10 per cent.

If the diverticula are few and are giving subacute symptoms, it is easy and safe to remove them separately, much the same as an appendix is removed, but if they are multiple, extensive resection, ileocolostomy, or colostomy is the practical surgical procedure. If a fistula is present, it should be cut across and the opening into the secondarily involved viscus closed, and, if possible, the involved section of the bowel should be resected with an end-to-end or an end-to-side anastomosis. If there is obstruction, either partial or complete, from hypertrophic peritonitis or mesenteritis, a colostomy is generally advisable above the diseased area, and at a secondary operation (when the acuteness of

the infection has subsided) a resection or a short-circuiting operation. In many cases the diseased section can be treated by a three-stage Mikulicz operation much more safely than by any one-stage operation. In some cases appendicostomy or cecostomy is of great benefit, since it prevents flatulent distention, and by frequent flushing of the large bowel stasis will be overcome and the colon content will be kept fluid or semifluid.

During acute manifestations of the disease the expectant treatment advised by Ochsner for appendicitis after the first twenty-four hours is advisable generally. Even if rupture takes place, general peritonitis seldom follows, and operations during the acute stage are frequently unsatisfactory, and furthermore, are followed by a much higher death-rate than the operations performed later.

In Table 1 are given the number of cases diagnosed in the Mayo Clinic and the various methods of treatment advised. Before 1914, when the value of the roentgen ray in diagnosis had not been realized, only the cases demanding surgical treatment and those accidentally found while operating for other conditions were recognized during life. Since 1914, many cases with very mild symptoms or without symptoms

TABLE 1
DIVERTICULITIS

	Patients, per cent.	Mortality, per cent.
Not operated on	173	
Resection	40 (34.48)	7 (17.5)
Mikulicz operation	38 (32.75)	5 (13.15)
Colostomy	13 (11.2)	0
Ileocolostomy	4 (3.44)	1 (25.0)
Removal of diverticulum	8 (6.89)	1 (12.5)
Exploration	8 (6.89)	0
Drainage of abscess	5 (4.31)	0

LOCATION OF DIVERTICULA IN PATIENTS OPERATED ON

	Patients, per cent.
Sigmoid	94 (81.03)
Rectum	5 (4.31)
Cecum	5 (4.31)
Descending colon	5 (4.31)
Transverse colon	3 (2.58)
Not located	4 (3.44)

have been diagnosed, in most of which medical management has been given, which consists in the regulation of the diet and bowels. Saline laxatives are particularly useful, since they tend to keep the content of the lower bowel fluid and prevent further dilatation of the existing saccules.

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MYOMA OF THE RECTUM: REPORT OF FOUR CASES*

VERNE C. HUNT

Very few cases of benign tumors of the intestinal tract are reported in the literature. Heurtaux, Steiner, Dewis, King, and others have written extensively on the subject, however, and have published cases of their own.

The tumors originate from the part of the intestinal wall which corresponds to the histologic structure of the various tumors; for example, adenomas from the mucosa, fibromas from the submucosa and serosa, lipomas from the fat cells of the external coat and from the appendices epiploicæ, angiomas from the vessels of the intestinal wall, and myomas, according to most investigators, from the muscularis or muscularis mucosa. In the benign tumors reported in the literature adenomas are the most frequent, angiomas most infrequent, and myomas comparatively infrequent.

In King's series of 119 cases the ileum and rectum are most often the sites of benign tumors. Dewis, in 1906, found 219 benign tumors of the intestinal tract, of which 101 were in the rectum; there were eighty-one adenomas, ten myomas, six lipomas, two fibromas, and two angiomas. In Dewis' series were forty myomas, ten in the rectum and thirty in the remainder of the intestinal tract. In 1917, King reported a series which contained forty-five myomas, of which eleven were in the rectum.

True myomas or pure muscle tumors are exceedingly rare; most tumors designated myomas contain varying amounts of connective tissue, and, depending on the relative amount of muscle and fibrous tissue, they have been called myomas, myofibromas, and fibromyomas. The first true myoma of the rectum diagnosed as such was reported by Vander Espt in 1881. However, in 1872, Malassez had described a tumor of the rectum showing the structure of a myofibroma. In an

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extensive review of the literature only twenty cases have been found since 1872 which can be classified definitely as myoma or myofibroma of the rectum.

Myomas have been found throughout the entire gastro-intestinal tract. Steiner collected twenty-one cases of myomas and myosarcomas of the stomach. The structure of these tumors is quite analagous to that of myomas of the uterus, and it might be supposed, because of the close proximity of the uterus and rectum, that the tumors in women are uterine in origin; however, the uterus was not found to be the origin in any of the reported cases. In eight instances the tumor originated from the anterior rectal wall, and in five instances from the posterior wall. The part of the rectum involved in the others was not stated. The tumors varied in size from about 2 cm. in diameter to 32.16 kg. in weight, the largest extended down over the buttock, and was about 15 cm. in diameter.

Rectal myomas have been classified internal or external, according to their projection into the lumen of the bowel, or externally into the perirectal structures. Six were definitely pedunculated and extended into the lumen of the bowel, the remainder, apparently, were deeply embedded and only encroached on the rectal lumen.

Many benign tumors of the intestinal tract are slow growing and symptomless; these are usually discovered accidentally in routine physical examinations or during operations for other conditions. Symptoms, when present, are usually mechanical, and are those of partial or complete obstruction; or hemorrhage occurs because of erosion. The predominating symptoms in the twenty cases were constipation, hemorrhage, and pain.

SYMPTOMS

	Cases.
Constipation.....	12
Hemorrhage.....	7
Pain.....	7
Rectal pain.....	6
Abdominal pain.....	1
Obstruction.....	3
Rectal irritation.....	2
Desire to stool.....	2
Sensation of mass in rectum.....	2
Tumor known to be present.....	4
No symptoms.....	3

The infrequency of intestinal obstruction, considering the size and location of some of these tumors, is striking.

The diagnosis was based on microscopic findings in ten cases; the diagnostic data were not stated in ten.

DIAGNOSIS		
	Cases.	
Myoma.....	5	
	3	2
	(Cases 2, 9, 15)	(Cases 3, 20)
Fibromyoma..	12	
	5	7
	(Cases 7, 8, 12, 14, 17)	(Cases 4, 5, 6, 10, 13, 16, 19)
Leiomyoma...	2	
	1	1
	(Case 11)	(Case 18)
Myoid.....	1	
	1	0
	(Case 1)	

The diagnosis in the four cases here reported was made by microscopic examination. Two of the tumors were true myomas and two were fibromyomas. In these cases constipation, difficulty at stool, and hemorrhage were the predominating symptoms. In one case bleeding had been profuse to the extent of reducing the hemoglobin to 20 per cent at the time of examination. The tumor originated from the anterior rectal wall in two cases and from the posterior rectal wall in two cases.

In the series of twenty cases reported in the literature and the four cases in the Mayo Clinic, thirteen were females and ten were males; the sex was not stated in one case. The youngest patient was 21, and the oldest 85; the average age was 45.6.

AGES BY DECADES

	Cases.
21 to 30 years.....	2
31 to 40 years.....	6
41 to 50 years.....	10
51 to 60 years.....	3
61 to 70 years.....	1
85 years.....	1

The tumors are often slow growing and may be present for years without symptoms. The duration of symptoms was stated in fifteen of the cases in the series.

DURATION OF SYMPTOMS

Shortest.....	a few weeks	
Longest.....	5 years	
		Cases.
Less than 6 months.....		4
Less than 1 year.....		5
2 years.....		3
3 years.....		3
4 years.....		2
5 years.....		2

Malignant change may occur; it was seen in Case A55082. Ulceration of the overlying mucosa was a striking finding, but it is not diagnostic of any tumor of the rectum. The differential diagnosis includes all the benign tumors of the rectum and usually cannot be made accurately without microscopic examination. A smooth overlying noninfiltrated mucous membrane often is present and favors a diagnosis of benign tumor rather than malignant. In our cases there was a tendency to ulceration, and in one case extensive excavation into the perirectal tissues. The tumors tend to recur, usually due to incomplete removal or malignant change.

ABSTRACTS OF CASES IN THE LITERATURE

Case 1 (Reported by Vander Espt). A woman, aged twenty-one years, in the seventh month of pregnancy noticed blood in the stools. She had also felt a tumor in the anus. At the time of delivery the tumor, about 3 cm. in diameter, appeared at the anus; it was smooth and bled easily from the covering of mucous membrane. The growth was removed by tying off the pedicle. Microscopic examination revealed smooth muscle fibers, and the growth was called a myoid.

Case 2 (Reported by Tédénat). A man, aged forty-six years, entered the l'Hotel Dieu de Lyon January 5, 1876. The patient was a full-blooded, vigorous man, who had lost blood from time to time during the preceding four years. Several hemorrhages had been very severe. He had had obstinate constipation, with a sensation of weight in the rectum, for five or six months before he came under observation. December 25, 1876, after he had been five days without bowel movement, his abdomen was distended and tender to pressure and he had severe colic. Examination disclosed a hard tumor, about 0.5 by 1 by 2 cm., situated 5 or 6 cm. above the anal margin on the posterior wall. On cutting the tumor after its removal irregularly disposed bundles of fibers and a few smooth muscle fibers were shown. A diagnosis of myoma was made. The patient made an uneventful recovery.

Case 3 (Reported by Berg). A man, aged fifty-six years, had been constipated for about ten years, and had had several severe rectal hemorrhages. Rectal examination disclosed a hard, round tumor, extending into the posterior wall and encroaching on the rectal lumen. The overlying rectal mucosa was ulcerated. The tumor, a myoma, was definitely encapsulated, and was readily removed through a Kraske incision.

Case 4 (Reported by Senn). A woman, aged forty-five years, had been conscious of a small pelvic tumor for three years. While she was being attended for a miscarriage

the tumor was felt between the rectum and the uterus. It was firmly attached. After two years the abdomen began to enlarge, and the patient's general health declined. At the time of her examination, April 20, 1890, she was anemic and emaciated, and her abdomen was distended with fluid. After the abdomen had been tapped and the fluid removed a large tumor could be palpated in the left lower quadrant of the abdomen. April 24, 1890, a laparotomy was performed and a tumor was found attached to the anterior wall of the rectum by a pedicle at the peritoneal reflexion over the rectum. It was nearly globular, weighed 12 pounds, and a cut surface showed a true fibromyoma.

Case 5 (Reported by Senn). A woman, aged forty-one years, was operated on through an incision in the vagina, and a fibromyoma about 3 cm. in diameter was removed from the anterior rectal wall.

Case 6 (Reported by McCosh). A man, aged thirty-four years, complained of discomfort in the rectum and gradually increasing difficulty in evacuating the bowels. The stools had become thin and ribbon-like, and at the time he was admitted to the hospital he had had very little bowel movement for twelve or fourteen days. A hard tumor was found on the posterior wall of the rectum, extending from just above the anus to the hollow of the sacrum. The mucous membrane over the tumor was smooth, but adherent to the tumor, which was smooth and regular in outline. The growth was thought to be malignant and a left inguinal colostomy was made. Later a hard, glistening, smooth tumor, adherent to the posterior surface of the rectum, was removed through a posterior incision extending from the anus to the coccyx. The enucleation was accomplished readily except at the attachment to the mucous membrane of the rectum, which was opened. Six weeks later the colostomy was closed. The tumor was about 10 cm. in diameter and proved to be a fibromyoma.

Case 7 (Reported by Heurtaux). A woman, aged thirty-seven years, was seen August 18, 1887. She had always been in good health except for a tendency to constipation, which had been worse during the preceding three years. For a month before her examination she had a constant desire to move the bowels, and for a few days there had been symptoms of obstruction, that is, abdominal distention and colic, and vomiting, at times fecal. On examination a smooth ovoid tumor was palpated within the rectum. The tumor had a distinct pedicle and was firm and elastic. A diagnosis of myoma was made, and the tumor was removed by dividing the pedicle. The obstruction was relieved. The tumor weighed 90 gm. and was 8 by 6 by 4.5 cm. in diameter. Histologic examination revealed a fibromyoma.

Case 8 (Reported by Heurtaux). The patient, a woman aged fifty years, was seen May 28, 1884. She had had attacks of intestinal obstruction for about ten days in 1872, and again in 1881. No further trouble occurred until May 28, 1884, when she felt severe pain in the anus and a pressing desire to go to stool, with no result. A rectal examination was made and a hard, round tumor was found and extracted. It was nearly spherical, and measured 6 by 6.5 cm. Microscopic examination revealed a fibromyoma.

Case 9 (Reported by Westermarck). A woman, aged forty-nine years, had experienced occasional pain, for a year and a half, in the abdomen and sacral region, radiating down the thigh. She had had slight frequency and constipation. Examination disclosed a solid tumor in the right lower quadrant of the abdomen. An exploratory laparotomy revealed a soft, smooth, fluctuating tumor, about 16 cm. in diameter, attached by a pedicle to the anterior rectal wall. Most of the tumor was lying to the right of the middle line. The patient died from obstruction on the fifth day after the operation. The tumor proved to be a myoma.

Case 10 (Reported by Riedinger). A woman, aged thirty-eight years, had had six normal deliveries and was at term at the time she was admitted to the hospital. She had been having abdominal pain for three weeks. Three abdominal tumors were palpable,

and a diagnosis was made of ruptured uterus. At operation a transverse tear was found in the lower segment of the uterus and the fetus was in the peritoneal cavity. The patient died nine hours after the operation, and at necropsy an irregular fibromyoma 12 by 20 cm. was found adherent to the upper part of the rectum. It had originated in the rectal wall and was not connected with the uterus.

Case 11 (Reported by Lexer). A man, aged thirty-five years, had suffered from constipation for a long time, and had had several hemorrhages from the bowels in the course of a few weeks. Examination revealed a rectal tumor, fixed to the sacrum, just above the anal sphincter and extending higher than could be reached. The overlying mucous membrane bled easily. The tumor was enucleated with much difficulty by sacrificing the anal sphincter, which necessitated a sacral anus. A section of the tumor was reddish gray. Microscopic examination proved it to be a true leiomyoma.

Case 12 (Reported by Carle). A man, aged eighty-five years, complained of constipation, the sensation of a tumor in the rectum, and pain at stool. Examination revealed a tumor about 5 cm. in diameter encroaching on the rectal lumen from the posterior rectal wall 4 or 5 cm. above the sphincter. It was hard and covered by nonadherent, somewhat ulcerated mucous membrane. It was enucleated, and microscopic examination showed connective tissue with interposed groups of muscle fibers. A diagnosis of fibromyoma was made.

Case 13 (Reported by Gradenwitz). A woman, aged forty-one years, came for examination complaining only of lumbago. To the left and behind the uterus was a tumor 5 cm. in diameter, apparently connected with the uterus by a thin pedicle. The tumor was suggestive of a pedunculated submucous myoma of the uterus or a solid ovarian tumor. An attempt was made to extirpate the tumor through the vagina. On opening the peritoneum the entire posterior wall of the uterus was found to be intimately adherent thereto. The tumor was high in the rectum, and was enucleated after dividing the rectal mucosa. The tumor was a fibromyoma.

Case 14 (Reported by Earl). A woman, aged forty years, was found, during labor, to have a tumor of the rectum. It was removed as the child's head approached the perineum. The tumor measured 8.7 by 6.5 by 5 cm.; it had only a membranous attachment to the rectum and was readily removed. It was composed of smooth muscle fibers, with a varying amount of fibrous tissue.

Case 15 (Reported by Becker). A woman, aged forty-four years, complained of obstinate constipation, which had been worse during the last two years. Within a year she had noticed a tumor in the vagina. Examination showed that the posterior wall of the vagina was pressed forward by a tumor in the rectal wall, separate from the uterus. The tumor was about 8 cm. in diameter and was removed through a posterior incision. Microscopic examination showed it to be a myoma with very little connective tissue.

Case 16 (Reported by Ball). In this case a fibromyoma was removed from the posterior wall of the rectum. The tumor, about 3 cm. in diameter, was sessile, and the overlying mucous membrane was freely movable. In structure it resembled a uterine fibromyoma.

Case 17 (Reported by Descoedres). A woman, aged forty-six years, came for consultation because of a bulging in the vagina which she had noticed for several years. The tumor had gradually increased to about 10 or 12 cm. in diameter. The left buttock and the posterior surface of the thigh were enlarged. The mucous membrane of the anus was drawn out to cover a portion of the tumor, which was somewhat irregular, apparently multilocular, and extended the entire length of the anterior and left wall of the rectum. The tumor was enucleated by blunt dissection and found to be attached to the rectum by a pedicle. It was a fibromyoma weighing 6 kg., and had undergone slight hyaline degeneration.

Case 18 (Reported by Verhoogen). A man, aged fifty-five years, entered the hospital because of constipation and severe rectal hemorrhage. On the anterior surface of the rectum, just behind the prostate, was a slightly movable, spherical tumor, about 10 cm. in diameter and covered by smooth, nonadherent mucous membrane. The tumor, which was causing entire obstruction of the rectum, was enucleated through a transverse perineal incision without injury to the rectal mucosa. It proved to be a leiomyoma.

Case 19 (Reported by Cripps). A woman, aged forty-eight years, had suffered with slight bowel irritation for six months. Examination under ether disclosed a swelling about 2.5 cm. in diameter in the anterior wall of the rectum, 7.5 cm. from the anal orifice. This swelling was apparently in the muscular coat; the mucous membrane covering it was intact and was slightly movable over the mass. At operation the rectum was split in the middle line behind, and the tumor drawn down and dissected from the muscular wall. The growth was a thickened lump of the muscular coat converted into dense fibrous tissue.

Case 20 (Reported by Finsterer). A man, aged fifty years, had had difficulty in bowel movements for six years, and passage of blood for six months. Examination revealed an ulcerated tumor, about 8 cm. in diameter, arising from the anterior wall of the rectum. The tumor was a myoma and was extirpated by removing the rectum.

CASES FROM THE MAYO CLINIC

Case 21 (A53082). A man, aged sixty-eight years, came for examination May 16, 1911. He complained of distress and dull pain in each groin, constipation, and urinary difficulty. Rectal examination showed a very hard mass, about 5 cm. in diameter, on the anterior rectal wall. The patient did not remain for further examination or treatment. He returned to the Clinic December 30, 1916. Constipation had persisted, and recently he had noticed that the rectum did not feel empty after stool. He had had acute retention of urine three times during the last three weeks and frequency.

There was moderate hypertension, the systolic blood pressure was 160; the diastolic was 105. The patient had a double inguinal hernia. Rectal examination showed that the tumor had increased to about 10 cm. in diameter. It extended to the left and was outside the rectum.

January 11, 1917, the tumor was removed through the perineum without opening the rectum or bladder (E. S. Judd). The tumor bulged into the rectum and involved the rectal mucosa, starting just above the anus. The prostate could be felt above. The tumor was a fibromyoma and weighed 330 gm. The patient made a good recovery. He returned to the Clinic February 20, 1918, and said that he had had no urinary difficulty since operation, but that constipation had recurred. Rectal examination showed multiple small tumors of the anterior rectal wall. These were excised March 1, 1918. The specimens showed early sarcoma and the wound was left open for radium, which was given as follows: March 13, 1918, 500 mg. hours, April 20, 1918, 700 mg. hours, November 13, 1918, 400 mg. hours, January 14, 1919, 300 mg. hours, and February 4, 1919, 800 mg. hours.

At our last examination, February, 1919, there were three nodules on the anterior rectal wall (Figs. 77 and 78).

Case 22 (A115182). A woman, aged twenty-eight years, was first examined in the Clinic June 7, 1916, when a diagnosis was made of inflammatory disease of the pelvis. She returned April 26, 1918 because of irritation in the left side of the rectum. There was tenderness in both vaginal fornices and an indurated mass in the rectovaginal septum. The patient was operated on June 6, 1918 (J. C. Masson). In exploring the rectovaginal mass it appeared to be inflammatory, but on microscopic examination of a specimen it proved to be a fibromyoma, apparently of rectal origin (Figs. 79 and 80).



FIG. 77 (Case A53082).—Photomicrograph of fibromyoma of the rectum ($\times 50$).

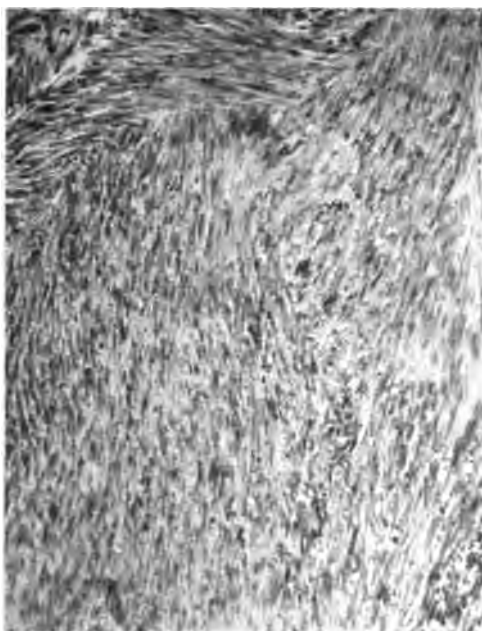


FIG. 78 (Case A53082).—Photomicrograph of fibromyoma of the rectum ($\times 100$).

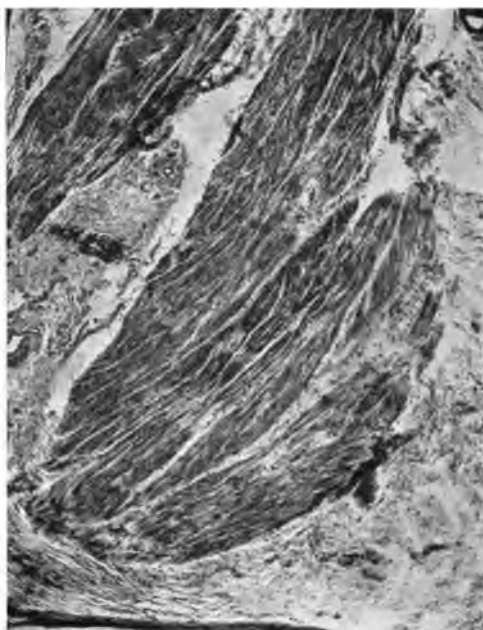


FIG. 79 (Case A115182).—Photomicrograph of fibromyoma of the rectum ($\times 50$).

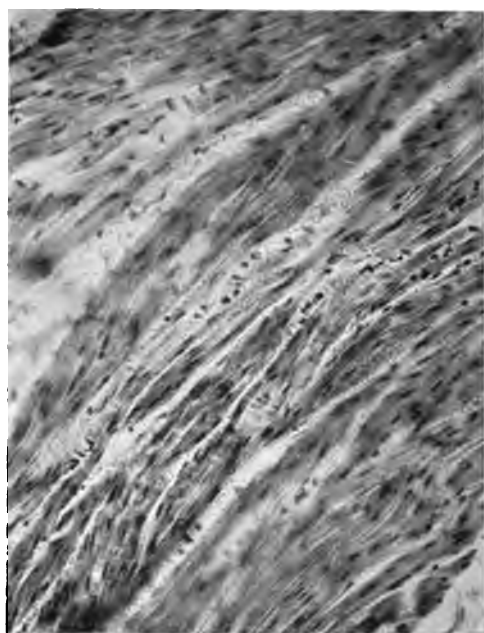


FIG. 80 (Case A115182).—Photomicrograph of fibromyoma of the rectum ($\times 100$).

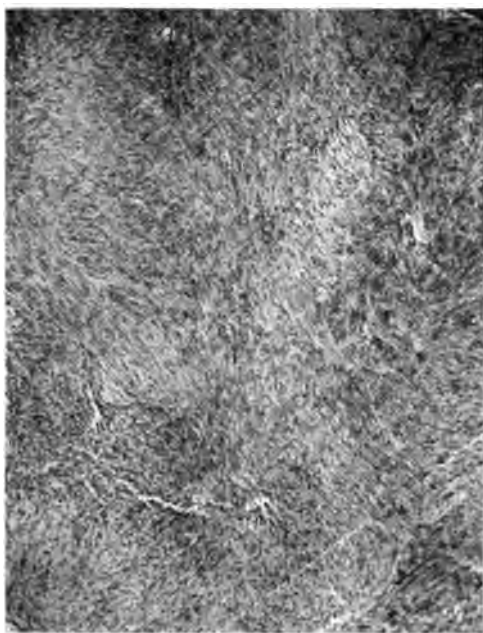


FIG. 81 (Case A295358).—Photomicrograph of myoma of the rectum ($\times 50$).

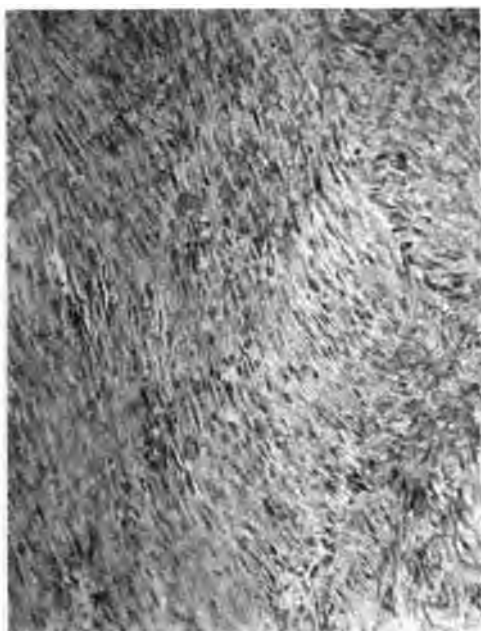


FIG. 82 (Case A295358).—Photomicrograph of myoma of the rectum ($\times 100$).



FIG. 83 (Case A308866).—Photomicrograph of myoma of the rectum ($\times 50$).



FIG. 84 (Case A308866).—Photomicrograph of myoma of the rectum ($\times 100$)

Case 23 (A295358). A man, aged fifty-nine years, was examined November 3, 1919. He complained of difficulty at defecation for the last six or seven months, and a feeling of obstruction in the rectum. There had been no bleeding or diarrhea.

The systolic blood pressure was 100; diastolic was 70. The temperature and pulse were normal. The urinalysis, the roentgenograms of the kidneys and bladder, the cystoscopic examination, and the blood Wassermann reaction were negative. The phenol-sulphonephthalein output was normal.

The patient was sent in for operation (W. J. Mayo) November 18, 1919, with a diagnosis of rectal tumor, probably myoma. Exposure was obtained through a posterior incision with removal of the coccyx and terminal portion of the fifth sacral vertebra. The growth was posterior to the rectum, extending laterally toward the bladder, and inside the true rectal fascia, evidently beginning in the nonstriated tissues of the rectum; it was removed with the capsule, which was closely attached to the rectum. The tumor measured 9 by 6 by 6 cm., and examination showed cellular myoma.

The patient made a good recovery and was dismissed from the hospital on the tenth day, and from the Clinic on the twenty-fifth day after the operation (Figs. 81 and 82).

Case 24 (308866). A man, aged thirty-four years, had had three operations on the rectum elsewhere for tumor believed to be cancer. The last operation was performed January 15, 1920. He presented himself at the Clinic March 18, 1920, with the following history: In 1915, he first noticed difficulty in moving his bowels; this condition grew progressively worse and was associated with some pain. In 1916, he had an operation for hemorrhoids, with relief for one year. A diagnosis of cancer was then made and a second operation performed, followed by improvement for two years, when the symptoms recurred. Two operations were performed in January, 1920, procedures not stated. Blood had been noted in the stools at various times. The patient had not lost weight and his general health was good.

At the time of examination the patient weighed 175 pounds; he was very pale. The systolic blood pressure was 126; the diastolic was 78. There was a slight systolic murmur at the apex. About 2.5 cm. above the anal sphincter was an excavated mass involving chiefly the left rectal wall and extending up into the rectum about 10 cm. The mass was ulcerated and bled readily and extended into the perirectal tissues. The mucous membrane over the growth was smooth and not infiltrated. The tumor was thought to be nonmalignant and inflammatory.

Operation was performed March 20, 1920 (V. C. Hunt). The anal sphincters were divided posteriorly and a specimen of the growth removed for microscopic examination. The tumor, which proved to be a myoma, was entirely removed by enucleation and the cavity packed with iodoform gauze. The patient made a satisfactory convalescence. Radium was given rectally as follows: March 29, 1920, 560 mg. hours, April 2, 1920, 1,160 mg. hours, April 5, 1920, 1,762 mg. hours, a total of 3,482 mg. hours. The patient was allowed to go home, but was advised to return in three months. July 6, 1920, the rectal mucous membrane was smooth, and there was no evidence of recurrence. The sphincters were somewhat weak, resulting in partial incontinence. The hemoglobin was 44 per cent. Recent letters from the patient and from his local physician state that there is no recurrence. The patient is to return to have the sphincter muscles repaired (Figs. 83 and 84).

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UROGENITAL ORGANS

MODES OF INFECTION IN PYELITIS*

HENRY F. HELMHOLZ

Having spent several years studying various phases of the pyelitis problem, it has become very clear to me that a correlation of the clinical, pathologic, and bacteriologic findings must be established. Strange as it may seem, this really has not been accomplished. A short survey of the difficulties may prove profitable.

There is no correlation between the severity of symptoms and the pathologic findings. The former cannot be used at present as a means of localizing the infection. The same symptoms may be associated with cortical abscesses of the kidney, with infection of the pelvis, ureters, or bladder, singly or combined. In spite of the severe clinical course there are, at best, only few necropsies, in which the pelvis alone is found to be involved. Accordingly, it is impossible to make a diagnosis from the clinical picture alone, and if we had to rely on the lesions found at necropsy, pyelitis, uncomplicated by severe kidney lesions, would be extremely rare. The disease termed pyelitis, or pyelocystitis, or pyelonephritis, is very common. The symptoms of infections of the urinary tract are so bizarre that the diagnosis of pyelitis or pyelocystitis, according to common opinion, rests entirely on urinary findings. It must be granted that the examination of the urine in most instances will indicate a pathologic process somewhere in the urinary tract, but that is all; it cannot localize the lesion.

I am omitting from the discussion all the cases that are associated with a damming back of the urine and the rupture of abscesses into the urinary tract, and shall consider only the group of cases in which the urinary tract is unobstructed. In order to consider the evidence under headings that will aid in an understanding of the problems, the material has been grouped.

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1. Urinary cultures:
 - Bladder.
 - Ureter.
 - Necropsy:
 - Cortex.
 - Pelvis.
 - Bladder.
2. Pathologic anatomy:
 - Necropsy material.
 - Experimental material.
3. Blood cultures.
4. Experimental production of pyelitis:
 - By intravenous injection.
 - By intracystic injection.

In a recent article Langer and Soldin state that in a study of 138 patients they were able to isolate the *Streptococcus lacticus* in every instance in which repeated cultures were taken. The cultures were made only in liquid mediums and are, therefore, open to criticism. In a former series of experiments, carried on by Beeler and Helmholtz, the urine was found to be sterile in about 50 per cent of normal patients and in 30 per cent of the patients with parenteral infection; solid mediums were used. In so far as no cultures were made in liquid mediums, and Langer and Soldin emphasize the importance of liquid mediums for the growth of the *Streptococcus lacticus*, it was determined to repeat these experiments. The urines from seventy patients (thirty-five boys and thirty-five girls) were examined. In thirty cases (seventeen girls and thirteen boys) the urine was sterile in all mediums.

To summarize: In liquid mediums, cultures were sterile in fifty-nine of 108 instances, and in solid mediums in seventy-five of 108 instances. In only eight instances was it possible to identify the *Streptococcus lacticus*. This was done by its reaction in milk, as outlined by Dr. Hastings of the University of Wisconsin.

In only ten of 108 instances were there more than ten bacteria to the cubic centimeter in any of the specimens examined. Because of the difficulty of properly sterilizing the male and the female genitalia it may be justly assumed that the gross, as well as the slight, contaminations may be attributed to errors in technic, or to the possibility that a certain number of bacteria may be carried into the bladder with the catheters.

So far as bladder cultures concern the mode of infection, they would be important only if Langer and Soldin's premises were correct; namely, that the organisms present in the specimens obtained from the bladder always come from the kidney. Inasmuch as it is impossible under any circumstances to prove this, cultures of the bladder cannot be of use in helping to solve the problem of the mode of infection, but are of importance only in detecting an infection in the urinary tract.

Large series of cases of pyelitis have not been studied, except by cultures from the urinary bladder, and by this means all that can be determined is that the bacteria come from the urinary tract. It is acknowledged by all that it is practically impossible to differentiate, clinically, cystitis, pyelitis, and acute multiple abscesses of the kidneys. By means of ureteral catheterization we have advanced a step in being able to determine whether the infection is in the bladder or higher. Hinman, in his report of twelve cases, found that in six the bladder alone was involved. In the other six the pyelitis was unilateral in two cases and bilateral in four. In all six cases the bladder also was involved. Kretschmer and Helmholz, in a series of eleven cases, found bilateral involvement of the kidneys and of the bladder. Hinman very rightly says that his finding of simple cystitis in one-half of the cases speaks in favor of the ascending mode of infection as against the hematogenous. Ureteral catheterization affords very little help in determining the mode of infection in pyelitis, but if carried out in a sufficiently large group of cases of the different types, it shows the numerical distribution of infections of the bladder and kidney, and it may make possible a regrouping of cases, the features of which will differentiate cystitis from inflammation of the upper urinary tract.

Not only is the number of necropsies in cases of pyelitis relatively small, but in those performed there has been no satisfactory bacteriologic study. Moreover, it is only necropsies performed shortly after death that could be of any use in the study of pyelitis, since after death the colon bacillus rapidly penetrates into the various organs. In the literature there is practically no large series of cases that has been studied both bacteriologically and histologically. Inasmuch as it is impossible to diagnose clinically the involvement of a definite portion of the urinary tract, cultures made at necropsy could afford valuable information, but never more than to indicate the uppermost seat of involvement. In order to study the pathologic anatomy of pyelitis it is absolutely essential that these cultures be made.

The importance of bacteriologic studies is demonstrated by our pathologic studies of kidneys. These tissues were used for making serial sections of the pelvis of the kidney. No cultures of the different portions of the urinary tract were taken at necropsy. Clinically, the tissues were definite examples of pyelitis; grossly and histologically they showed, in the serial sections, an entirely normal pelvis. The results should have shown, therefore, that pyelitis may occur without a demonstrable inflammatory condition of the pelvis of the kidney at necropsy, but there is no definite reason why an inflammation of the pelvis should have been expected, since from the history and from the various examinations no definite localization within the urinary tract was possible. In other words, it was not certain that pyelitis was actually present. The pathologic report in so many cases of pyelitis is negative that it seems essential that bacteriologic studies should be made of the kidney pelvis and of the bladder in all cases of pyelitis that come to necropsy. These cases are so rare that only by making a group study of carefully controlled material will it be possible to reach any definite ideas with regard to the pathology. The problem is still further complicated by the fact that even at necropsy shortly after death the mucous membrane of the pelvis is found to be macerated by the urine, and specimens of urine withdrawn from the pelvis are practically always cloudy or purulent, but on microscopic examination show only a large number of desquamated epithelial cells indicating the rapidity with which the living mucous membrane is destroyed.

The pathologic findings of Thiemich are most often cited in the discussion of the pathology of pyelitis. A bacteriologic study was not made in his series of cases. His patients had abscesses of the cortex of the kidney and, as he particularly points out, no lesions of the pelvis and the bladder. One girl and one boy had acute lesions with abscesses; two other patients had lesions of a more chronic nature, showing focal sclerosis in the cortex. It has been the experience of most authors that abscesses of the cortex of the kidney in man are not caused by colon bacilli and, in the absence of any bacteriologic studies, it is fair to assume that these conditions were due to infections by one of the coccus group. Such being the case they are not concerned in this discussion.

The "pyelitis" most frequently observed at necropsy is that with lesions of the kidney. In another type death is caused by some intercurrent infection. In these cases, as a rule, no lesions are found macro-

scopically or microscopically. Most of these were not controlled bacteriologically and are, therefore, of very little use. One point to be emphasized in the histologic studies of Thiemich is the fact that, in spite of the large amount of infectious material that must have passed through the pelvis in his four cases, there was no involvement of the mucous membrane of the pelvis. This is in answer to those who maintain that the colon bacillus is rapidly excreted through the kidney and thence gains a foothold in the pelvis, where it remains only a very short time before it is carried on into the bladder. Only on the assumption that the colon bacillus finds ideal conditions for growth in the pelvis is it justifiable to make an assertion which no one has proved to be true. Furthermore, in those cases of renal involvement definitely secondary to lesions in the lower urinary tract there is usually such a marked destruction of tissue anatomically that the histology is of practically no use in helping us to solve the problem of the mode of infection. The majority of these cases are associated with some factor damming back the flow of urine.

The results of our histologic study of the two cases of pyelitis by serial sections of the pelvis serve as a warning to others of how not to make such studies, and emphasize again the necessity of localizing the infection to the pelvis of the kidney before attempting to study it histologically. It is much simpler to study the pathologic anatomy of experimental pyelitis. The reported findings tend to indicate that the pathologic picture is somewhat different in the pelvis of the kidney when the infectious material reaches it by way of the blood stream than when it reaches it by the ascending route. The experimental work of Helmholtz and Beeler³ in the rabbit showed that cortical lesions occur in a large percentage of the animals following hematogenous injection and that the inflammatory condition in the pelvis tends to localize in the papilla. This has been recently confirmed by Lepper, who was able to show that bacilli tended to localize in the capillaries of the papilla and to produce changes therein. In cases of lesions in the kidney caused by intracystic injections the acute lesions in the pelvis are essentially in the parietal portion of the mucous membrane and the papilla is usually free. In only one instance were cortical lesions observed. At present this is the only feature which permits a histologic distinction of hematogenous pyelitis from an ascending pyelitis.

David and Mattill, in their experimental work, repeatedly found

polymorphonuclear exudate in the submucosa of the pelvis and sterile urine on the same side. They emphasize the importance of differentiating periureteral and peripelvic infiltration and an infection of the urinary tract. In all our experiments in which we found peripelvic inflammation there was also found an infection of the urinary tract, as evidenced by the presence of bacteria and pus within the lumen of the pelvis.

The fact that in two-thirds of the infections of the pelvis, after intracystic injections, no periureteral infiltration was found, but only parietal peripelvic inflammation and pus in the pelvis, shows that here, too, is a histologic differentiation of the mode by which infection may travel from the bladder to the kidney. Further studies with serial sections should do much to clear up the present uncertainty with regard to the pathologic anatomy of pyelitis.

In the experimental production of pyelitis there is good evidence for the production of inflammatory conditions of the pelvis of the kidney, both by the hematogenous and the ascending routes. The hematogenous method is very frequently associated with abscesses in the cortex of the kidney, but also in numerous instances by a simple inflammatory condition of the pelvis. This has been accomplished by Bumpus and Meisser with streptococci isolated from carious teeth and in cases of pyelitis, by Helmholtz and Beeler,⁹ with an organism isolated from a spontaneous case of pyelitis in the rabbit. A large number of observers, for example, Eisendrath and Schultz, and many others, have shown that with partial obstruction of the urinary tract ascending infections can be readily produced. The work of David in the production of pyelitis with the unobstructed urinary flow without any periureteral or peripelvic inflammation and with a sterile hydro-nephrosis on the opposite side, shows very definitely the production of pyelitis by ascension through the lumen of the ureter. Experiments of Helmholtz and Beeler⁸ in rabbits with a normal urinary tract showed definitely that infection in some instances travels by way of the periureteral and peripelvic lymphatics and, in some instances, directly by way of the ureteral lumen. This latter is in accord with the observations of Kretschmer and others, that regurgitation of urine from the bladder into the ureter, under normal conditions, does occur. With an inflamed, thickened bladder wall around the ureteral valve, regurgitation can take place even more readily.

The presence of the colon bacillus in the blood stream has been

used as one of the main reasons for assuming the hematogenous route of infection of the pelvis. Numerous observers, such as Kowitz, Cabot and Crabtree, Trumpps, and others, have demonstrated the colon bacillus in the circulating blood. They consider this finding sufficient to accept the hematogenous route of infection of the kidney as a fact. Recently Lepper has shown that experimental bacteriuria may be present for many days without any organism appearing in the urine. This is diametrically opposed to the frequently quoted experiments of Biedl and Kraus which are open to criticism because of the possible injury to the kidney caused by the introduction of catheters into the ureters. The experiments of Cabot and Crabtree are of particular interest because the blood cultures were positive when the urine was sterile and followed shortly after colon bacilli could be demonstrated in the urinary tract. There can be no question that pyelitis and cortical lesions of the kidney can be produced in the animal by the hematogenous route, by organisms of the coccus as well as of the colon group. The exact mode by which the organisms reach the pelvis and produce inflammation is still open to question, although in all likelihood it is not by way of the usual excretory channels, but by way of the capillaries of the papilla. Various authors seem to think that the demonstration of the possibility of the hematogenous route of infection excludes any other route of infection.

With regard to the direct passage of organisms from the intestinal canal to the kidney by way of the lymphatics, it does not appear that there has been sufficient evidence brought forward to warrant a discussion at this time. In view of the manner in which the lymphatic system develops, there is a possibility of a direct connection persisting in some cases.

The clinical term pyelitis has been used to describe a great variety of pathologic conditions, all associated with the common symptom of pyuria. Clinically, it is impossible to differentiate the different forms involving the kidney cortex, pelvis, ureter, and bladder, singly or together. The pathologic anatomy of these various forms of pyelitis is not well established, and does not, at the present time, allow us to determine the mode of infection, except in those cases marked by cortical abscesses of the kidney. Only by a careful correlation of the findings obtained by bacteriologic and pathologic study, as well as by experimental work, can we hope to reach a better understanding of this problem.

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NEPHRITIS AND URINARY CALCULI FOLLOWING THE EXPERIMENTAL PRODUCTION OF CHRONIC FOCI OF INFECTION: PRELIMINARY REPORT*

EDWARD C. ROSENOW AND JOHN G. MEISSER

During the course of numerous experiments on the localization of bacteria from various diseases instances of extremely specific effects were noted. Some of these observations suggested that certain chronic diseases not generally believed to be due to infection might be reproduced if a more or less continuous supply of bacteria could be furnished through a focus of infection, and if the elective localizing power and the property to incite certain specific reactions could be maintained; two requirements which are difficult to fulfill when bacteria are grown on artificial mediums. Acting on these ideas we performed a series of experiments in which the pulps of teeth in dogs were removed and the pulp chambers infected with freshly isolated bacteria from various diseases. We shall herewith describe briefly the method of conducting the experiments and report on results obtained in two diseases, nephritis and nephrolithiasis.

Eighteen vigorous, well-nourished dogs were selected. Catheterized specimens of urine were normal in all. Roentgenograms of the kidney region in the experiments on nephrolithiasis were negative when the experiment was begun. In devitalizing and infecting the teeth the animals were covered with a sterile sheet and kept under ether anesthesia by the intratracheal method. A rubber dam isolated the teeth to be worked on, the two lower cuspids in four dogs and the four cuspids in ten. The teeth were scrubbed and sterilized with alcohol and tincture of iodine, then cut off with sterile bone nippers midway between the incisal edge and the gum margin. The pulps were carefully removed with sterile broaches and, after the hemorrhage had ceased, the bacteria in dense suspension were introduced into the

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pulp chambers with fine capillary glass pipettes. The canals were then sealed with impervious dental cement. These animals and the control animals whose teeth were not infected were placed under hygienic conditions and fed a balanced diet of dog biscuit and meat. Catheterized specimens of urine were examined at intervals in all the experiments and, in addition, roentgenograms were made of the kidney region in the experiment on nephrolithiasis.

One kidney was removed from each dog in from fifty-one to one hundred four days after infection of the teeth, to afford opportunity to compare the findings in the kidneys removed with the findings in the other kidneys at necropsy.

In the experiments on nephritis the teeth of four dogs were devitalized and infected with a staphylococcus from the nose and tonsils of a patient with advanced nephritis. This strain had a marked affinity for the kidneys of rabbits and produced pronounced lesions on intravenous injection.

Two sets of experiments on nephrolithiasis were performed, the first on two dogs, the second on twelve dogs. In the dogs in the first experiment and in four dogs in the second experiment the teeth were infected with streptococci isolated repeatedly from the urine of a patient with typical attacks of renal colic due to stones. The teeth of four other dogs in the second experiment were infected, as controls, with a mixture of streptococci from arthritis; and as additional controls, four dogs whose teeth were not infected were observed.

The duration of the experiments on nephritis ranged from sixty-three to one hundred fifteen days in the series on nephrolithiasis, from eleven to one hundred twenty-three days in the six dogs infected with the nephrolithiasis strain, from five to one hundred twenty days in the four infected with the arthritis strains, and from fourteen to one hundred twenty days in the controls in which the teeth were not infected. The four dogs in the experiments on nephritis developed lesions in the parenchyma of the kidneys. In three the lesions were more pronounced in the kidney examined at necropsy; in the other dog the reverse was true, and healing was well advanced. The lesions in the kidneys were essentially focal in character, often widely disseminated, and in some instances a large part of the parenchyma of the kidney was involved. The location and type of cellular infiltration and other changes resembled closely those of acute interstitial nephritis which occurs often with infectious diseases. In one of these dogs marked

cystitis and pyelitis, with secondary infection, were found, and in the adherent membranous exudate marked calcareous deposits had occurred.

The staphylococcus was isolated at the end of the experiment from the focus and the kidneys of the dogs. It manifested elective localizing power for the kidneys of rabbits when injected intravenously. It was demonstrated in the lesions and proved absent in the normal portion of the kidney.

Striking as the findings in the kidneys were, the general picture in the dogs was somewhat different from that of patients with advanced nephritis. The dogs lost markedly in weight, they had no edema, and the urine contained relatively little albumin and few casts. However, the character of the lesions indicated that if the experiments had been of longer duration the picture might have become more like that of well advanced nephritis.

Five of the six dogs infected with the streptococcus from the urine of the patient with nephrolithiasis developed calculi; the sixth dog died too soon for stones to form. Calculi were found in both kidneys in four dogs. The size varied from small concretions to stones measuring 3 by 7 mm. They were roughly proportional to the duration of the experiment. The findings in these dogs resembled those in patients in this condition. The stones were hard, angular and rough, and of a chemical composition similar to those in nephrolithiasis in man. The evidence of infection of the urinary tract and the lesions in the kidney were slight, except where obstruction in the ureter had occurred from impacted stone.

The causal relationship between the calculi and the streptococcus inoculated into the teeth seems established. The organism was isolated from the kidneys, from some of the stones, and from the teeth of the dogs, and its elective affinity for the medulla of the kidneys in rabbits on intravenous injection was demonstrated; it was found in the lesions of collecting tubules where crystallization and stone formation were beginning. None of the four dogs in which the teeth were infected with streptococci from arthritis developed stone, nor did any of the four additional control dogs which were kept under the same conditions, but whose teeth were not infected. The urine in all of these eight dogs remained normal and the kidneys had no focal lesions.

Stones of the character obtained in these experiments were not found in another series of fourteen dogs which were kept under similar conditions and whose teeth were devitalized and infected with strains

other than those from nephrolithiasis and nephritis, nor in a single instance in the examination of more than five hundred dogs in connection with other experiments.

It is not clear why the four dogs infected with the streptococcus of arthritis failed to develop arthritis. There was active infection around the teeth in all instances, and the staphylococcus from the pulp chamber in one of the dogs inoculated four months previously retained its affinity for the joints of rabbits on intravenous injection. It would seem, therefore, that the joints of these dogs were not affected because of high resistance of these structures to invasion by this organism during the relatively short duration of the experiment, and not to encapsulation or loss of specific localizing power.

The experimentally produced foci of infection, aside from being the source of the organisms which localized electively, appeared to have a marked general deleterious effect. The dogs lost markedly in weight, lost much hair, and became susceptible to intercurrent infection. An active process was found in the devitalized and infected teeth at the end of the experiments. The findings around the teeth were similar to those following the artificial devitalization of teeth in man. The infected teeth became discolored, but remained firmly in place in the alveolar sockets; the infection caused rarefaction and absorption of bone in the periapical region, without swelling, pain, or tenderness. The character of the cellular infiltration and the distribution of the bacteria of well-formed granulomas were also strikingly similar.

The details of these experiments and further results along this line will be published elsewhere.

FOCI OF INFECTION IN CASES OF PYELO- NEPHRITIS. STUDY II *

HERMON C. BUMPUS, JR. AND JOHN G. MEISSER

In the report of a recent study² we attempted to show that pyelonephritis may often be due to focal infections and that the colon bacillus, which is usually found in the urine and believed to be the cause, is a secondary infection. In this work we injected laboratory animals with cultures obtained from possible foci in patients with pyelonephritis and demonstrated the selective localization of these bacteria for the urinary tract. We desire now to report further progress in this study, and to give the results obtained in a series of six additional cases, with especial attention to one typical case. This will be reported in full and the results only will be given in the twelve cases.

Because of the almost constant presence of colon bacillus in the urine of patients suffering from pyelonephritis attention has been centered almost entirely on it as the cause of the disease. The apparent direct lymphatic connection between the kidneys and the colon has led many research workers and clinicians to consider these lymphatics as the pathway of renal infection, and a colon teeming with bacteria an ever constant source from which the urinary tract may be infected. The natural inclination to ascribe to oral sepsis, which is frequently the cause of other infections, a contributory rôle in pyelonephritis was rejected because colon bacilli are rarely isolated from such foci and their predominance in cases of pyelonephritis seems to exclude such a theory. Rosenow, however, by his experimental work on the elective localization of streptococci, opened a field of investigation far reaching in its variety of application. The increasing evidence that bacteria are carried by the blood to the kidney and excreted, as demonstrated by Brown, Cunningham, and others who obtained tuberculosis bacilli from

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the urine of patients who had pulmonary tuberculosis, but no renal lesions, and the well known fact that the urine of patients with typhoid fever contains typhoid bacilli, indicate that renal infections may be of hematogenous origin.

That the organisms which reach the kidney and produce lesions later resulting in a colon bacilluria may be other than colon bacilli was suggested by LeFur. He attempted to produce vesical ulceration in laboratory animals by the intravenous injection of various bacteria. The results were so unsatisfactory that the intravenous injection was abandoned and the organism was injected directly into the bladder or into the perivesical space. Ten different strains of bacteria, including the streptococcus, pneumococcus, colon bacillus, and so forth, were used. When the colon bacillus was injected it was recovered in pure culture; when other organisms were injected the colon bacillus was frequently recovered with the injected organism. In three cases the colon bacillus alone was recovered, even though a different organism had been injected in pure culture. This is certainly suggestive evidence that the colon bacillus may be a secondary invader, and considered with the well-known fact that any disturbance in the urinary tract, such as the presence of a stone, a stricture, or a prostatic obstruction, is generally followed by a colon bacillus infection, makes the possibility of its playing a similar secondary part in cases of pyelonephritis seem credible.

With this idea in mind we selected patients with pyelonephritis in whom possible foci were demonstrable. In the search for such foci the patients were carefully examined for evidence of past as well as present oral sepsis.

The examination of the teeth included not only roentgenograms to demonstrate the presence of apical abscesses and devitalized teeth, but also careful examination of all teeth by means of the pulp tester to ascertain their viability. This was done because in making routine cultures of extracted teeth we have found that at the apices of pulpless teeth pure cultures of a green-producing streptococcus may be isolated even when the roentgenograms do not show evidence of periapical infection. It is not generally appreciated that there may be a vast number of organisms around a devitalized tooth before they destroy sufficient bone to make their presence manifest in the roentgenogram. We believe, therefore, that it is a mistake to exclude the teeth as a possible focus of infection simply because apical abscesses are not demonstrable by the roentgen ray. The same may be said of the tonsils.

The fact that they are not enlarged and that pus cannot be expressed from them does not exclude them as possible foci, and it is our custom to have tonsillectomy performed in all cases in which the urinary infection may possibly be of focal origin. Since we have adopted this procedure a surprisingly large number of apparently negative tonsils have been found to hide deep-seated virulent infections.

In cultures obtained from the extracted teeth green-producing streptococci were always isolated, while from the tonsils a more varied flora was obtained which, however, always included a green-producing streptococcus.

Rabbits were injected intravenously with from 3 to 5 c.c. of such cultures. In order to be certain that the selective localization of these streptococci was not due to their incubation in artificial mediums or to an overwhelming dosage resulting from their increase in numbers, salt solution suspensions of tonsillar tissue were injected without incubation in several cases. In order to ascertain that the colon bacilli in the urine of patients did not possess specificity for renal tissues, pure cultures made from the urine of patients prior to the eradication of their foci were injected intravenously into nine rabbits, and necropsies performed. In none of the animals could lesions of the kidney be demonstrated. This finding is in keeping with the work of Helmholtz and Beeler who injected colon bacilli obtained from patients into sixty-six rabbits and obtained lesions in the kidney in only eight. The technic employed in isolating the bacteria and injecting the animals was that used by Rosenow in similar studies. The material from the infected teeth or tonsils and from the urine was spread on the surface of blood-agar plates and inoculated into tall tubes of glucose-brain broth. The cultures were incubated at from 35 to 37 C. The injections, from 3 to 5 c.c., were made intravenously with the primary culture in glucose-brain broth as soon as profuse growth had occurred, usually in from twelve to twenty-four hours. The viability and identity of the organisms injected were determined by plating on blood-agar. The growth thus obtained was then compared with that obtained on the blood-agar inoculated directly. The animals were anesthetized usually from three to six days after inoculation and thoroughly examined for lesions. Cultures were made as a routine on blood-agar plates and in glucose-brain broth from the lesions and from the blood, bile, urine, joint fluids, kidneys, and spleen. The character of the lesions was determined by studying sections stained with hematoxylin and eosin, and

the causative organism was identified in the lesions by Gram's stain. In the earlier cases the cultures thus recovered were again injected into other animals and produced like lesions of the kidney. In some cases a third animal passage was made. This was not done in the second series of experiments because of the scarcity of rabbits at the time.

Following the extraction of the suspected foci an acute exacerbation of the urinary symptoms usually occurred, accompanied by chills of more or less severity, and a rapid rise of temperature. We have regarded such reactions as clinical manifestations of the specificity of the bacteria released from the removed focus, and believe that such increase in the severity of the disease should be considered favorably and an indication that the right focus has been eliminated. The correctness of this supposition was enhanced by the fact that prior to the eradication of the suspected foci only colon bacilli were obtained from the urine cultured, and that following the eradication of the foci streptococci appeared for a time. Specimens of these mixed cultures from the urine containing both colon bacilli and streptococci were injected intravenously into ten rabbits and lesions of the urinary tract occurred in six, although when the colon bacilli alone were injected lesions did not result.

The six patients in this series had symptoms of the usual type of the disease. The duration of symptoms varied greatly; the shortest was three weeks, following an attack of tonsillitis; the longest was seven years. In two of the patients tonsillitis and influenza were considered possible etiologic factors; in four the clinical histories gave no suggestion of the source of the infection. In all the patients a cystoscopic examination was made; the urine from the kidneys was infected.

Cultures were made from both teeth and tonsils of one patient; from the tonsils of two; and from the teeth of three. These seven strains of bacteria were injected intravenously into twenty-six rabbits, twenty-one of which showed lesions in the kidneys at necropsy. There were lesions in both kidneys and in the bladder in two, and lesions in the ureter in one. There were, also, four lesions in the muscles, one in the stomach, and one in the gallbladder. The extra-urinary lesions were relatively slight compared with those of the urinary tract.

The catheterized urine from the rabbits was normal before injection; after injection a small amount of albumin with relatively few red blood cells, epithelial cells, and a larger number of leukocytes were usually present.

The kidneys of the animals were about normal in size, or slightly swollen. In no instance was there a picture of diffuse parenchymatous nephritis, but always of localized infection. The capsule stripped readily in all. The cortex often presented small, opaque, yellowish-white areas, and on section the cut surface often revealed marked swelling and edema, especially of the medulla, sometimes associated with areas of hemorrhage varying in size from 1 to 4 mm. Varying numbers of ne-



FIG. 85 (Case 344376).—Section from rabbit's kidney showing necrotic area with marked leukocytic infiltration four days after intravenous injection of cultures of streptococci from an infected tooth.

crotic areas were found in the medulla, some areas so small they were scarcely visible, others large grayish-white streaks, necrotic-like in appearance, and gradually disappearing as they approached the cortex. These areas were surrounded by zones of congestion and hemorrhage. In only one instance was a hemorrhagic lesion found in the ureter.

On microscopic examination no evidence of diffuse nephritis was found. The glomeruli were almost wholly free from lesions other than

varying degrees of congestion. The necrotic areas showed marked destruction of the epithelium and marked leukocytic infiltration (Fig. 85). The parenchymatous cells immediately surrounding these areas were often granular and swollen, and the nuclei of many failed to take the stain. Sections stained by Gram's method contained varying numbers of gram-positive diplococci, singly, in groups, or in short chain

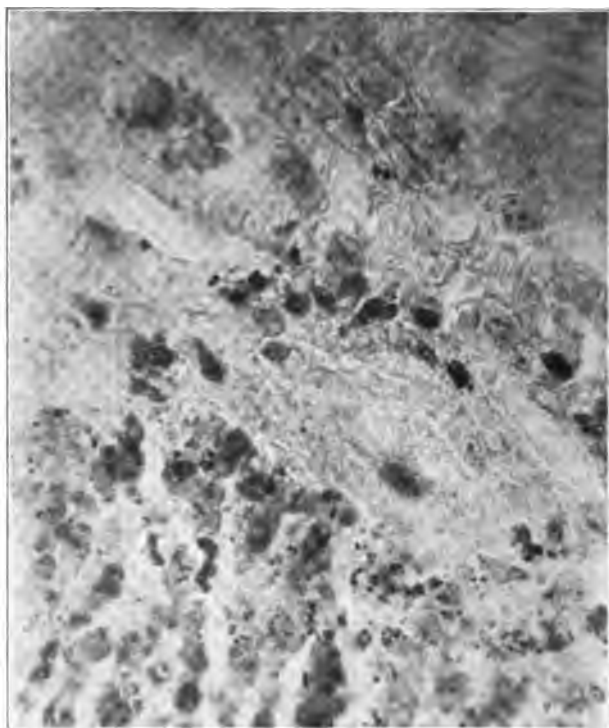


FIG. 86.—Diplococci and streptococci in and around the leukocytes in the necrotic area shown in Figure 85.

(Fig. 86). The leukocytes often contained many diplococci in various stages of digestion, depending on the duration of the experiments.

REPORT OF A TYPICAL CASE

Case A344376. Mrs. M. H., aged forty-five years, came to the Clinic complaining of bladder trouble. Three weeks before, at the onset of her menstrual period, she had noticed a slight irritation at the neck of the bladder and burning at the end of urination. Two or three days before she had stayed up all night with a daughter who was suffering with tonsillitis. She became chilled, and had a sore throat for the next few

days. The bladder trouble grew gradually worse, and she called the local physician, who attended her for the next two weeks, during which time her temperature ranged from 99 to 104.5; the night before she came to the Clinic it was 104.5. She complained very little of pain except at the end of urination; she felt a slight soreness around the crest of the right ilium. A cystoscopic examination had been made two days before, and inflammation was found around the right urethral orifice. Colon bacilli were recovered from the urine. A diagnosis was made of mild cystitis.

Examination revealed slight tenderness in the left abdomen and over the crest of the right ilium. The temperature was 101. Four teeth revealed evidence of periapical infection in the roentgenograms, one was devitalized, but the roentgenogram was negative, and two had cavities of sufficient size to expose the pulps. From the tonsils, which were not greatly enlarged, fluid pus was expressed.

An occasional red blood cell and a large amount of pus were found in the urine. Stained specimens were negative for *Bacillus tuberculosis*. Roentgenograms of the urinary tract were negative. Two cystoscopic examinations, made before the suspected foci were removed, showed that the bladder was negative, but the urine recovered from the kidneys contained pus and gave a pure culture of gram-negative bacilli. Three rabbits were injected with cultures of these bacilli and in none could evidence of lesions be found. The day after the second cystoscopic examination two of the teeth with apical abscesses were removed, and cultures were made on blood-agar plates and in glucose-brain broth. In both green-producing streptococci were isolated on the blood-agar plates. A few colonies of staphylococci were also present. Three rabbits were injected; all had lesions of the kidney and one had multiple minute hemorrhages in the right ureter near the pelvis of the kidney. Streptococci in pure culture were recovered from these lesions. The patient experienced no immediate reaction, as often occurs following the extraction of infected teeth, although for the next few days her temperature reached 101.

Six days later three other teeth were removed, including one which did not show evidence of apical infection in the roentgenogram, but it had been devitalized and the root canal was filled. All gave pure cultures of green-producing streptococci. These were injected into three rabbits resulting in lesions of the kidney in two, one of which had been injected with bacteria from the devitalized but otherwise negative tooth. The third rabbit did not have lesions. The day following the removal of these teeth the patient had a severe chill, and her temperature reached 106; profuse sweating and falling temperature followed. During this reaction a blood culture was taken and large numbers of green-producing streptococci were recovered. Two rabbits were injected intravenously with this culture. Both developed lesions in the kidneys, and cultures made from these lesions yielded green-producing streptococci, while cultures from the gallbladder, blood, spleen, liver, and so forth, were negative.

The febrile attack was so acute and severe that doubt was expressed with regard to its renal origin. The possibility of its being a respiratory infection was suggested, although there were no pulmonary symptoms. In order to clear this point cultures were injected directly into the trachea of five guinea-pigs. At necropsy no pulmonary lesions were found, but in one guinea-pig the kidneys and ureter were markedly involved.

Urine obtained from the bladder the day of the chill, the day following, and on the fourth day contained only colon bacilli. On the fifth day, however, the patient being sufficiently recovered to permit of cystoscopy, the urine obtained from the kidney and bladder contained occasional streptococci, but it contained colon bacilli in far greater numbers.

Samples of the mixed cultures were injected into five rabbits; three developed lesions of the kidneys. Streptococci and colon bacilli were recovered from the lesions in two rabbits, the three remaining had lesions in the intestines.

In order to study the relative ability of the two organisms to grow in urine a twenty-four-hour sample of the patient's urine was autoclaved on three different occasions, and after being proved sterile, samples were inoculated and incubated with colon bacilli, some with streptococci, and some with both. It was found that while the colon bacilli multiply readily the streptococci have no such ability and only a few more than were planted could be recovered. We believe this explains the reason for the frequent absence of the etiologic organism in the urine of patients with pyelonephritis. Occasionally, as in a case reported by Kretschmer, secondary colon bacillus infection does not occur and streptococci are found in pure culture.

Eighteen days after the second extractions the patient's remaining infected teeth were removed without incident. Pure cultures of streptococci were recovered. Four animals were injected; two developed lesions of the kidney, one very pronounced; one had lesions of the joints and one of the muscles. Pure cultures of streptococci were recovered from all the lesions, the unaffected organs being sterile.

During the intervals between the extraction of the teeth cystoscopic examination of the patient was made four times, and at each examination pus cells were found in the urine from the kidney, and cultures therefrom contained colon bacilli; a few streptococci were also found after the second extraction.

After all of the patient's infected teeth had been removed six cystoscopic examinations were made. The specimens of urine from the kidneys were free from pus, and on culture a gram-negative bacillus was the only organism found. Cultures made at each successive cystoscopic examination yielded fewer organisms; the last one, which was taken at the time of the patient's dismissal, one month after the last of the septic teeth had been removed, contained only fifteen colonies on a blood-agar plate from urine from the right kidney; cultures from the left kidney were negative.

During the time pus was found in the urine from the kidneys the pelvis was lavaged with a 1 per cent solution of silver nitrate, but after the disappearance of the pus following the extraction of the last teeth only boric acid was employed.

A specimen of the patient's voided urine was brought to the Clinic one month after her dismissal. It was negative except for three pus cells to the microscopic field. Her physician stated that she was free from symptoms, had had no fever, and was planning to return to the Clinic for tonsillectomy.

CONCLUSION

A summary of the results in our second series of cases, with the results in the six cases previously reported, shows that eighty-two rabbits were injected with strains of a green-producing streptococcus obtained from the teeth, tonsils, urine, and blood of patients suffering with pyelonephritis, and that in sixty-three of the animals lesions of the kidneys were found. This, we believe, is evidence for concluding that pyelonephritis may often be due to focal infections harboring streptococci which have a selective affinity for the urinary tract, and that the colon bacillus, which is commonly found and generally believed to be the cause, is of secondary importance.

RESULTS FROM ANIMAL INOCULATIONS

Streptococci from teeth and tonsils.	Strains of streptococci.	Animals injected.	Animals with lesions in									
			Kidney.	Bladder.	Kidney and bladder.	Joints.	Muscles.	Stomach.	Gallbladder.	Endocardium.	Myocardium.	Intestines.
<i>First study.</i>												
On isolation	6	27	24	8	8	4	4	3	0	3	2	0
Second animal passage	3	11	7	2	1	0	1	1	0	0	1	0
Third animal passage	2	6	3	0	0	0	0	0	0	0	0	0
<i>Second study.</i>												
On isolation	6	26	21	2	2	4	4	1	1	0	0	0
<i>Streptococci from</i>												
Patient's blood	1	2	2	0	0	0	0	0	0	0	0	0
Patient's urine	3	10	6	2	0	0	1	1	0	0	0	3
Total	...	82	63	14	11	8	10	6	1	3	3	3

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ON THE PREVENTABILITY OF CERTAIN CASES OF CHRONIC NEPHRITIS*

REGINALD FITZ

Three authoritative and stimulating papers referable to chronic nephritis and its problems have been published recently. Christian has discussed the deficiencies in our present methods for the treatment of this disease and has shown clearly that present therapy is largely symptomatic and is based on our knowledge of renal function rather than on anything deeper. Preventive treatment is almost nonexistent and will remain so until more is known of the etiology of chronic nephritis, and particularly of the factors that influence the progressive development of renal lesions.

Mackenzie has pointed out that almost all medical research in the recent past has been restricted chiefly to laboratories and in a less degree to hospital wards, where disease has been studied only after it has reached an advanced stage or after it has killed the patient. In Mackenzie's judgment the future of medicine does not depend so much on research work under these conditions as on observations made in the earliest stages of the disease when its course may be amenable to treatment or mitigation.

Finally, Joslin has written on the prevention of diabetes mellitus. This paper is one of the first to deal specifically with the prevention of any chronic progressive disease of unknown etiology. Yet Joslin produces facts to prove that diabetes in many cases is a preventable disease and states that the physician should consider it as important to prevent diabetes as to prevent small-pox or typhoid fever.

These three papers are very suggestive: The first because it emphasizes how unsatisfactory is the present method of treatment of chronic nephritis and because it hints at what the second discusses in greater detail; namely, certain fallacies in our present methods of clinical research; and the third because it shows how a chronic and progressive disease of unknown etiology, such as diabetes, may be preventable in

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many persons. It would seem possible that nephritis, also a chronic and progressive disease, may be preventable in many persons if only its problems are attacked from a new angle and early in its development instead of late.

So critical a pathologist as Mallory believes that chronic nephritis is due originally to a toxic lesion which is of several varieties, but is most commonly bacterial. The initial lesion is usually acute, but may be recurrent or chronic. It may terminate in complete recovery if the patient survives or in a more gradual sclerosis in the capsular space, glomeruli, or blood vessels as the result of the process of repair. Sclerosis of the kidney, as it appears at necropsy, is the sum total of sclerosis affecting parts or the whole of many or all of the units of the kidney and is due to repeated acute or chronic toxic insults.

There is increasing bacteriologic evidence to support the belief that chronic nephritis is often of infectious origin. Davis, for example, cultured the tonsils from ten cases of nephritis and in nine found hemolytic streptococci to be the predominating organism. Le Count and Jackson injected rabbits with streptococci from cases of acute tonsillitis and found renal lesions in more than half of their inoculated animals. They believed that these organisms besides causing acute nephritis also produced a characteristic chronic disease of the kidney in a certain number. Klotz injected various strains of *Streptococcus viridans* into rabbits and was able to produce a form of acute interstitial nephritis which developed subsequently into well-marked renal sclerosis. As a result of such experiments attempts have been made to treat nephritis by the removal of possible foci of infection. Billings reported six cases which were greatly improved after tonsillectomy. Crowe, Watkins, and Rothholz followed the course in eighteen cases of varying degrees of severity from seven months to three years after the tonsils were removed. Two patients with advanced nephritis died, the operation having had no obvious effect on the disease. The other patients were much improved or well. Finally, the work of Bumpus and Meisser shows that pyelonephritis is often due to a diseased tooth or tonsil harboring streptococci which have a selective affinity for the urinary tract, and that the colon bacillus which is commonly found in the urine of such patients and which is generally believed to be the cause of the disease is of secondary importance. Removal of the original focus, in their experience, has been followed by great improvement in the condition of the genito-urinary tract.

On the whole there is considerable evidence from pathologic, bacteriologic, and clinical standpoints to show that chronic nephritis begins as an infection which is often influenced by organisms found in diseased teeth and tonsils, and that removal of such foci of infection may be followed by general improvement. In view of these facts it has seemed of interest to follow a group of patients with nephritis for a period of several years in an attempt to collect evidence with regard to the early development and possible prevention of chronic nephritis. For this purpose the records of all persons under forty in whom a diagnosis of nephritis had been made were selected from the records of the Mayo Clinic for the year of 1918. This age limit was arbitrarily fixed in order to exclude as far as possible arteriosclerotic nephritis and to include the more inflammatory type of glomerulonephritis. The year 1918 was chosen because it allowed between two and three years to pass since the patients were first seen, and because at that time in the Clinic most of these patients received a special throat examination and a phenolsulphonephthalein test besides the routine physical examination, blood pressure determination, and urinalysis. Letters of inquiry were sent to the thirty-two patients so selected.

The material which is the subject of this paper can be logically divided into two groups; one consisting of cases of true nephritis with definite signs, and the other of cases of less marked nephritis in which the proper diagnosis was at first uncertain, although the presence of albuminuria and of renal elements in the sediment suggested that kidney disease was the underlying cause of the symptoms which were encountered (Table 1).

Fifteen of the patients were males; eight are known to be dead. On looking over the records it is clear that all but one had a bad prognosis from the moment they were first seen. One patient (Case 8) had had a tonsillectomy performed. Information was not obtainable concerning the effect of this operation on the course of the disease. The patients in Cases 2 and 5 deserve special note.

Case 5.—The patient had evidence of mild nephritis which seemed to be markedly exaggerated by a gastro-enterostomy for duodenal ulcer. It is possible that this case was analogous to those following gastro-enterostomy described by Tucker, and that the exacerbation of the kidney disease was derived from duodenal proteose. In any event as the patient died a month after operation, the surgical operation was not a useful preventive measure.

Case 2.—The patient entered the Clinic in 1918 with a history suggestive of early nephritis. At that time his renal function was nearly normal. The phenolsulphonephthalein excretion was high, there was no fixation of specific gravity, and there was evidence in the sediment of considerable cellular exudation. His tonsils were not removed despite the fact that they were enlarged and draining pus. He returned fifteen months later with signs of marked renal insufficiency, with a diminished phenolsulphonephthalein output, a low fixed specific gravity, and with little in the sediment except rarely a cast. Necropsy showed a typical chronic parenchymatous nephritis. This patient might have been benefited by early tonsillectomy.

The seven patients who are still alive had their tonsils removed, and all except one are strikingly better. The patient in Case 15 gave a history in 1918 of edema and headache dating back about eighteen months. This patient has not improved. He finds it difficult to work; his urine contains albumin; and his blood pressure is appreciably higher than it was when he first was examined.

Of course it is unjustifiable to draw conclusions from these data, as the condition in the tonsillectomized patients was more acute and less advanced than in those who were not operated on and died, and would possibly have recovered spontaneously. However, the fact remains that the tonsillectomized patients have not progressed in their nephritis and, therefore, the operation was harmless and may have been a good therapeutic and prophylactic measure (Table 2).

The six women with true nephritis are strikingly different from the men, as all but one developed symptoms of kidney disease during pregnancy; two of these died, one, who had been tonsillectomized, dying of nephritis in the eighth month of a later confinement. The other patient was not operated on and died of rapidly progressing Bright's disease.

One of the three patients who are still alive has been tonsillectomized. Her urine is normal and she is leading an active life, although her blood pressure is still elevated. The other two patients are not improving. Neither has been tonsillectomized. One probably has essential hypertension and the other chronic progressive nephritis.

These five cases illustrate the importance of pregnancy as an etiologic factor in nephritis in young women. It is possible that this type of the disease can be prevented in many cases by early diagnosis. During pregnancy routine urine and blood pressure examinations should be

TABLE 1
CASES OF PROBABLE NEPHRITIS IN MALES

Case.	Age.	Date of entry.	Previous history.	Present illness.	Tonsils.	Systolic blood pressure.	Diastolic blood pressure.	Urinalysis.					Phenolsulphone.	Tonsillectomy.	Subsequent course.
								Albumin.	Specific gravity.	Casts.	Erythrocytes.	Leukocytes.			
A220062	26	1-26-18	Diphtheria, scarlet fever, grippe.	Nausea and vomiting 2 years. Shortness of breath a few weeks.	No record.	214	148	Large trace.	1.008	Few.	Rare.	Rare.	5	No.	Died of nephritis 3 months later.
A226274	32	3-6-18	Diphtheria, tonsillitis, gonorrhea.	Swelling of legs 2 months.	Slightly enlarged. Drain pus.	120	80	Large amount.	1.026	Many.	0	Rare.	60	No.	Died of nephritis 15 months later.
A245887	16	9-16-18	Chronic rheumatism.	General edema 18 months.	Slightly enlarged. Plugs of mucus.	140	86	Large trace.	1.015	Few.	0	Rare.	25	No.	Died 2.5 years later. Cause of death not recorded.
A247630	28	10-3-18	Grippe.	Nocturia and headache 6 months.	Slightly enlarged. Plugs of mucus.	220	110	Large amount.	1.015	Rare.	Moderate.	0	25	No.	Died of nephritis 4 months later.
A249152	37	10-21-18	Diphtheria, tonsillitis, gonorrhea.	Operation for duodenal ulcer. Developed edema and scites immediately afterward.	Not enlarged. Plugs of mucus.	118	68	Large trace.	1.016	Rare.	Moderate.	Numerous.	No record.	No.	Died a month later. Cause of death not recorded.
A212976	32	8-20-18	Diphtheria.	Dyspnea 2 months.	Much enlarged. Drain pus.	240	130	Large amount.	1.014	0	Numerous.	Rare.	15	No.	Died 3 weeks later. Cause of death not recorded.
A231359	33	6-16-18	Scarlet fever, pneumonia, gonorrhea.	Pain in chest and dyspnea 7 months.	Not enlarged. Plugs of mucus.	110	60	Large amount.	1.014	Many.	Many.	Many.	No record.	No.	Died 9 days later. Necropsy showed ulcerative endocarditis and chronic nephritis.
A227155	25	4-6-18	Grippe and gonorrhea.	Life insurance examiners diagnosed kidney disease 2 yrs. before. Easily tired and short of breath for 1 year.	Slightly enlarged. Plugs of mucus.	150	90	Large amount.	1.015	Few.	0	Rare.	30	4-10-18	Date and cause of death not known.

A230196	17	8-2-18	Scarlet fever.	Swelling of face and feet immediately after scarlet fever 3 weeks before.	Much enlarged. Drain pus.	152	100	Large amount.	1.012	Rare.	Many	Many.	30	1-27-19	Feels well. Urine reported normal. Works full time. Gained 40 pounds.
A236603	8	6-27-18	Whooping-cough, scarlet fever.	Albuminuria after scarlet fever 8 months before.	Slightly enlarged. Plugs of mucus.	116	78	Trace.	1.017	0	0	0	No record.	7-10-18	Feels well except for headache while studying. Urine improved. No record of blood pressure. Works full time.
A252752	30	12-5-18	Typhoid fever.	Edema and headache for 18 months.	Slightly enlarged. Drain pus.	136	78	Large trace.	1.018	Few.	Rare.	Rare.	50	12-10-18	No endurance. Albumin in urine. Blood pressure 145. Not improved.
A247192	24	9-30-18	Scarlet fever, grippe, tonsillitis; nephritis with dropsy after scarlet fever 16 years before.	Rejected from army for albuminuria. Feels in perfect health	Absent.	160	110	Large trace.	1.024	Rare.	0	0	50	1914	Great improvement in general condition following tonsilectomy. No change in past 3 years. Urine reported unchanged. Works full time. Has gained 10 pounds.
A225017	24	3-16-18	Grippe.	High blood pressure for 3 years with intermittent albuminuria. Palpitation on exertion.	Much enlarged. Drain pus.	164	100	Trace.	1.014	0	0	0	60	4-2-18	Feels well now. Urine reported normal. Blood pressure a little elevated. Works full time.
A247286	12	9-30-18	Measles, scarlet fever, tonsillitis.	Sudden and persistent edema following tonsillitis 5 months before.	Slightly enlarged. Drain pus.	200	130	Large amount.	1.020	Many.	0	Rare.	No record.	5-6-19	Feels well. Urine reported "slowing very little." Works full time. Gained 20 pounds.
A233204	10	6-1-18	Mumps, measles, tonsillitis.	Edema, nausea, vomiting, and convulsions developing 6 weeks before.	Slightly enlarged. Plugs of mucus.	120	82	Large trace.	1.016	0	Many.	Rare.	No record.	6-27-18	Feels well. Urine reported normal. No record of blood pressure. Works full time.

TABLE 2
CASES OF PROBABLE NEPHRITIS IN FEMALES

Case.	Age.	Date of entry.	Previous his- tory.	Present illness.	Tonsils.	Systolic blood pressure.	Diastolic blood pressure.	Urinalysis.					Phenol- sulphon- phthalein.	Tonsillectomy.	Subsequent course.
								Albumin.	Specific gravity.	Cast.	Erythro- cytes.	Leuko- cytes.			
A229799	27	5-2-18	Tonsillitis and grippe.	Edema and convul- sions with preg- nancy 3 years be- fore. Epileptiform convulsions since.	Slightly en- larged. Plugs of mucus.	140	100	Trace.	1.017	0	0	0	50	5-10- 18	Died of nephritis in eighth month of pregnancy. 16 months after exami- nation.
A230051	32	5-3-18	Scarlet fever and tonsillitis.	Edema and convul- sions 18 months before when preg- nant; weakness and edema since.	Slightly en- larged. Plugs of mucus.	150	116	Large trace	1.007	0	Rare.	Few.	15	No.	Died of nephritis 16 months after exami- nation.
A236784	32	7-5-18	Tonsillitis.	Albumin and edema with pregnancy 2 years before. Weak and tired.	Slightly en- larged. Plugs of mucus.	200	135	Large trace.	1.012	0	0	0	50	No.	Not improving. Un- able to work. Urine albumin free but of low specific gravity. Blood pressure: sys- tolic 200; diastolic 110.
A222495	26	2-18-18	Negative.	Edema with preg- nancy which ended 6 weeks before.	No record.	125	60	Trace.	1.022	Few.	Rare.	Rare.	55	No.	Not improving. Un- able to work. Swell- ing of legs; back- ache. No record of urine or blood pres- sure.
A176780	21	3-18-18	Frequent tonsillitis.	Edema and head- ache in fifth month of pregnancy.	Slightly en- larged. Plugs of mucus.	154	116	Large amount.	1.012	Few.	Rare.	Rare.	No record.	3-28- 18	General condition good. Urine normal. Blood pressure: sys- tolic 146; diastolic 86. Able to work full time. Tired; back- ache.
A48525	21	10-22-18	Diphtheria, pneu- monia, tonsillitis, grippe.	Nervous; tires easi- ly. Lost 15 pounds in 3 months.	Slightly en- larged. Plugs of mucus.	130	86	Large trace.	1.025	Few.	Few.	Rare.	50	11-6- 19	General condition im- proved. Urine "eco- nomic" albumin, blood cells, leucocytes. Blood pressure: sys- tolic 164; diastolic 106.

insisted on, and the ordinary rules of hygiene should be enforced. A woman with a history of renal insufficiency during one pregnancy who later becomes pregnant should be watched with special care. Finally, symptoms of impending renal insufficiency should receive immediate treatment.

The sixth patient in this group has been under constant observation for three years and has been treated vigorously with a view toward the prevention of chronic nephritis (Table 3). It appears that the patient has a progressive nephritis which has not been influenced by the removal of diseased tonsils, gallbladder, or appendix. It remains to be seen whether the removal of two teeth which show definite periapical abscesses will be of any benefit.

As a whole, these twenty-one cases are of considerable interest. They illustrate the gravity of nephritis in young persons; the importance of pregnancy as an etiologic factor in women; the fact that all cases are not progressive and that a certain proportion of patients recover. They suggest that there are two definite methods for the possible prevention of chronic nephritis. The first is by surgical removal of sources of renal infection in early cases; the second is by proper medical supervision of pregnant women.

The cases in the second group are less sharply defined. They consist of young persons who presented themselves for examination on account of an indefinite train of symptoms, such as headache or backache, recent loss of weight and strength, or a general sensation of lassitude. Physical examination was negative except for a slight peripheral arteriosclerosis or hypertension. The urine, however, uniformly contained albumin and varying amounts of casts, erythrocytes, or leukocytes. It was impossible to determine at the time these patients were first seen whether they had true nephritis or were merely tired out and needed rest and hygiene. The details of this group is shown in Tables 4 and 5.

The most striking feature of the patients as a whole is the fact that none have so far developed definite signs of chronic nephritis. These cases appear, therefore, to bear much the same relation to Bright's disease that "renal glycosuria" does to diabetes, and afford no evidence with regard to whether chronic progressive nephritis ever begins in such an indefinite fashion. It would be of great interest to follow a larger group of such patients for a much longer time.

A second striking point concerning these patients is that all but one

TABLE 3
COURSE OF PROBABLE NEPHRITIS IN PREVENTIVE TREATMENT FOR CHRONIC NEPHRITIS

Case.	Age.	Date of entry.	Previous history.	Present illness.	Tonsils.	Systolic blood pressure.	Diastolic blood pressure.	Urinalysis.						Phenol-sulphone-phthalein.	Tonsillectomy.	Subsequent course.
A48525	29	10-22-18	Diphtheria, pneumonia, tonsillitis, grippe.	Nervous. Tires easily. Lost 15 pounds in 3 months.	Slightly enlarged. Puget of mucus.	130	86	Albumin.	Specific gravity.	Casts.	Erythrocytes.	Leukocytes.		50	27	
		1-6-19						Large trace.	1.025	Few.	Few.	Rare.				
		1-15-19														Tonillectomy.
		7-31-19				128	82	Large trace.	1.024	Rare.	Few.	Rare.		40		
		10-30-19						Large trace.	1.017	Rare.	Rare.	Rare.		40		
		1-23-20				140	84	Large trace.	1.015	Many.	0	Rare.		45	23	
		1-10-21				148	100	Large trace.	1.019	Rare.	Rare.	Rare.		55	41	
																Cholecystectomy, appendectomy.

TABLE 4
CASES OF INDEFINITE NEPHRITIS IN MALES

Case.	Age.	Date of entry.	Previous his- tory.	Present illness.	Tonsils.	Systolic blood pressure.	Diastolic blood pressure.	Urinalysis.						Phenol- sulphone- phthalein.	Tonsillectomy.	Subsequent course.
								Albumin.	Specific gravity.	Casts.	Erythro- cytes.	Leuko- cytes.				
A242817	31	8-29-18	Tonsillitis and pneu- monia.	Backache and noc- turia.	Moderately enlarged. Drain pus.	115	78	Large trace.	1.033	Rare.	0	Rare.	55	No.	Complaints of languor and backache as be- fore. Urine normal. Blood pressure: sys- tolic 126; diastolic 83.	
A251907	15	11-29-18	Pneumonia, whoop- ing-cough, measles, and tonsillitis.	Chronic nocturia.	Much en- larged. Plugs of mucus.	146	90	Large amount.	1.016	Rare.	0	Rare.	50	No.	No complaint, but un- der treatment by chiropractor for kid- ney trouble and ar- thritis. Urine con- tains no albumin. No record of blood pressure.	
A235280	14	6-18-18	Measles.	Recurrent attacks of vomiting and head- ache.	Much en- larged. Plugs of mucus.	145	100	Large trace.	1.017	Rare.	Rare.	Rare.	70	6-27- 18	Feels well. Has not seen doctor since operation.	
A242023	20	8-28-18	Tonsillitis and grippe.	Nocturnal emissions.	Slightly en- larged. Plugs of mucus.	150	80	Large trace.	1.033	0	Rare.	Rare.	60	8-17- 18	Feels well. No record of urine or blood pressure.	
A247877	28	10- 9-18	Pneumonia and grippe.	Headache and pain in legs.	Slightly en- larged. Plugs of mucus.	170	80	Large trace.	1.028	Rare.	0	0	55	No.	Feels well. Urine normal. No record of blood pressure.	
A250501	17	11- 8-18	Negative.	Lumbar pain.	Right, tags. Left, out.	120	60	Large trace.	1.015	0	Rare.	Rare.	50	1919	Feels well. Urine con- tains a few erythro- cytes. Blood pres- sure normal.	

TABLE 5
CASES OF INDEFINITE NEPHRITIS IN FEMALES

Case.	Age.	Date of entry.	Previous history.	Present illness.	Tonsils.	Systolic blood pressure.	Diastolic blood pressure.	Urinalysis					Phenolsulphonephthalein.	Tonsillectomy.	Subsequent course.
								Albumin.	Specific gravity.	Casts.	Erythrocytes.	Leukocytes.			
A250693	39	11-12-18	Tonsillitis and grippe.	Chronic gastric flatulence and nocturia.	Slightly enlarged, plugs of mucus.	120	86	Large trace.	1.010	0	0	Rare.	60	No.	No change in symptoms. Urine normal. Blood pressure: systolic 130.
A231702	25	5-17-18	Negative.	Chronic indigestion.	Slightly enlarged, Drain pus.	110	75	Large trace.	1.025	Few.	0	Rare.	No record.	No.	No change in symptoms. Passed through pregnancy. No record of urine or blood pressure.
A219177	14	1-15-18	Diphtheria and tonsillitis.	Constant frontal headache.	Slightly enlarged, Drain pus.	100	75	Large trace.	1.027	0	Rare.	Rare.	No record.	3-23-21	Feels well. No record of urine or blood pressure.
A244977	17	9-7-18	Tonsillitis and grippe.	Attacks of precordial pain for 1 year.	Slightly enlarged, Drain pus.	138	70	Trace.	1.021	0	0	0	No record.	9-11-18	Feels much better. No record of urine or blood pressure.
A225716	28	3-28-18	Tonsillitis, pneumonia, grippe.	Backache and headache.	Normal.	110	36	Large trace.	1.017	0	0	0	No record.	No.	Feels well. No record of urine or blood pressure.

had definitely abnormal tonsils. The closeness of the relationship between septic tonsillitis, albuminuria, and the vague symptoms complained of is questionable. However, five of the ten patients with diseased tonsils had tonsillectomies, and five did not. It is interesting that only one of those not operated on (Case 5) should feel well now, while all of the five patients operated on should be normal so far as they know with the exception of one (Case 6), who has a few red blood corpuscles in his urine.

SUMMARY

This review of the course of a limited number of young persons with symptoms of nephritis over a period of about three years brings out a few interesting features. In the first place, the material divides itself sharply into cases of true nephritis and into cases in which a diagnosis is impossible. Preventive measures against the development of true nephritis can be logically undertaken. Septic teeth and tonsils undoubtedly play a part in the speed with which the disease develops, and should be removed. In this connection, however, it must be remembered that normal tonsils and teeth should not be sacrificed indiscriminately. Furthermore, the removal of teeth or tonsils from a nephritic patient may be a serious operation and may be followed by an acute exacerbation of the disease with oliguria and uremia. Therefore such operations should not be performed without due consideration and the patients should be prepared by a preoperative course of treatment. The nephritis of pregnancy is such an important etiologic factor in this series as to justify the generalization that all pregnant women should have most careful medical supervision and any signs of impending renal insufficiency should be treated at once, thus probably preventing the development of chronic nephritis in a certain number of cases.

Finally, there are large numbers of young adults with albuminuria but with indefinite symptoms of nephritis who do not develop a rapidly progressive type of kidney disease. The exact relationship of such cases to chronic nephritis is uncertain and requires further study. They offer a possible means for observing the early manifestations of a slowly contracting kidney.

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ATROPHIC PYELONEPHRITIS*

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The type of chronic renal infection most often observed is bilateral pyelonephritis. The usual clinical course of this condition is a progressive chronic urinary infection with continuous frequent micturition, dysuria, and a moderate degree of intermittent pain referred to either renal area. Although doubtlessly in a large number of patients the condition eventually disappears, it usually persists and the patient succumbs after many years with symptoms of terminal renal insufficiency. At necropsy the kidneys are found to be somewhat smaller than normal and characteristic, pathologically, of interstitial nephritis and to have many areas of round-cell infiltration and a slight degree of dilatation of the renal pelvis and ureter.

Pyelonephritis is, as a rule, not regarded as a surgical disease of the kidney for two reasons: (1) acute infections usually resolve spontaneously and (2) chronic infections are almost always bilateral and respond in greater or lesser degree to medical treatment. Unilateral pyelonephritis, which does not respond to medical treatment, becomes a surgical condition and usually demands nephrectomy. The several forms of pyelonephritis which may be considered surgical are unilateral acute septic pyelonephritis, pyonephrosis, and atrophic pyelonephritis. I shall discuss the last condition in this paper.

Atrophic pyelonephritis is distinguishable from chronic bilateral pyelonephritis from both clinical and pathologic points of view. The urinary symptoms are less severe and are usually not progressive; the pain is unilateral and may be more severe, and is often accompanied by evidences of acute renal infection. Usually but one kidney is affected, and, when removed, it is found to be greatly reduced in size. The atrophy may be confined largely to one-half of the kidney. On section marked cicatricial changes are apparent. There is often a well-marked

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dilatation of the renal pelvis, although to a much less degree than that found with primary hydronephrosis.

Twenty-eight patients have been observed at the Mayo Clinic on whom a diagnosis of unilateral atrophic pyelonephritis was made; twenty-two were operated on. In contrast to bilateral pyelonephritis, which predominates markedly in the male, it was found to occur in seventeen female patients and eleven male patients. The onset of symptoms appeared in the fourth decade in twenty-two patients (80 per cent). The average age was thirty-eight years. The average duration of symptoms was six years and four months.

CLINICAL DATA

Symptoms.—Unilateral pain referred to the area of the kidney is probably the most common subjective symptom. The pain is described either as a dull ache persisting for a short period or appearing in acute attacks. It was present in twenty-six patients. It was described as acute in ten patients, and dull and prolonged in sixteen. It was referred largely to the renal area in seventeen patients and to the upper abdomen in five. The pain, in several patients, did not appear until after vesical symptoms had persisted over a period of many years. Frequent micturition and dysuria, the usual symptoms, were present in twenty-five patients. Although these symptoms were persistent with the majority of patients, with several they had become dormant at the time of examination; with others they recurred at intervals. Hematuria of slight degree and evidently of vesical origin occurred in five patients. Definite attacks of fever and chills and other evidence of acute renal infection recurring at irregular intervals were present in eight patients.

Physical examination.—The general physical examination is usually negative, except, of course, during the acute attacks. In two cases a fistula persisted from previous drainage of the kidney. In one case there was evidence of a recent perinephritic abscess. Urinalysis in twenty-five cases demonstrated the presence of pus cells; the urine in three was negative. In the majority of cases the amount of pus was only moderate. The total renal functional tests were normal in every case. Coincident infection in other organs was noted in several cases. Foci of infection, such as dental sepsis and infected tonsils, were found in practically all patients in whom they were searched for.

The importance of primary foci of infection such as may exist in the teeth or tonsils has recently been emphasized by the experiments of

Bumpus and Meisser.* A careful search should therefore be made in order to safeguard the remaining kidney, and if any focus exists it should be removed.

CYSTOSCOPIC DATA

The diagnosis of atrophic pyelonephritis is best established by means of cystoscopic data. In this condition, in contrast to bilateral pyelonephritis, the bladder is usually found on cystoscopy to be involved only to a moderate extent, or not at all. It is not unusual to find evidence of more or less chronic infection around one opening, although in



FIG. 87 (Case A282396).—Pelvis and calices obliterated by atrophic changes.

some cases it may appear quite normal. Evidence of diminished renal function may often be inferred from the occasional feeble spurt of urine, as compared with hypersecretion from the normal side. The urine from the affected side may be turbid, although in some instances it is fairly clear. The uretral catheter rarely meets with any obstruction in its course to the renal pelvis where there may be a slight amount of residual urine. The rate of secretion from the atrophic kid-

*Bumpus, H. C., and Meisser, J. G.: Focal infection and selective localization of streptococci in pyelonephritis. *Arch. Int. Med.*, 1921, xxvii, 326-337.

ney may be perceptibly less than that on the normal side. The urine catheterized from the affected kidney usually contains only a moderate number of pus cells and occasionally none. The urine from the opposite kidney was found to be normal in all but one patient in whose urine a moderate number of pus cells was found.

The differential renal functional test probably offers the data of greatest clinical significance. The phenolsulphonephthalein return from the affected kidney is markedly less than normal, often only a faint trace, while from the normal kidney there is evidence of hyper-



FIG. 88 (Case A235566).—Reduction in size of calices and pelvis as result of chronic atrophic pyelonephritis.

trophied secretion. The contrast afforded by the marked unilateral diminution in renal function and the slight evidence of infection are the clinical data which might be regarded as pathognomonic of atrophic pyelonephritis (Fig. 87).

The pyelogram also offers data which are often suggestive of atrophic pyelonephritis. As might be expected from the condition, the outline of the renal pelvis and calices is frequently much smaller than normal. When, however, there is a secondary dilatation of the renal pelvis and of the ureter the evidence of atrophy may become effaced. Dilatation

of the ureter is occasionally noted, together with a contracted pelvic outline. In only a few cases was the outline of the pelvis in the pyelogram regarded as normal (Fig. 88).

DIFFERENTIAL DIAGNOSIS

Atrophic pyelonephritis may be most easily confused with (1) duplication of the renal pelves, (2) wide stricture of the lower ureter, and (3) chronic renal tuberculosis.



FIG. 89 (Case A223011).—Atrophic pelvis. Calices practically obliterated.

Pelvic duplication.—It has been demonstrated that the upper pelvis, with duplication of the renal pelves, is usually about one-half the size of the lower pelvis. On cystoscopic examination it is very easy to overlook the second opening, and if the inner ureter leading to the upper pelvis is catheterized the resulting pyelogram will demonstrate the outline of the small upper pelvis, which could easily be mistaken for an atrophic kidney (Fig. 89).

Stricture of the ureter.—With a wide stricture of the lower ureter there may be resulting atrophy of the kidney accompanied by a mod-

erate degree of dilatation of the ureter and pelvis. The ureteral catheter may not meet with obstruction, and slight dilatation visible in the pyelo-ureterogram may be regarded as secondary.

Renal tuberculosis.—The chronic cicatricial type of tuberculosis may develop insidiously and lack any of the clinical data which are usually observed. The process then has a tendency to encapsulate; it slowly encroaches on the adjacent renal tissue, so that the kidney gradually atrophies and becomes largely cicatricial. The cystoscopic examination usually discloses evidence suggestive of tuberculosis, although the findings may make it indistinguishable from atrophic pyelonephritis.



FIG. 90 (Case A216837).—Atrophic pyelonephritis with almost complete fibrosis of kidney and kidney pelvis.

The demonstration of tuberculosis bacilli in the urine will of course identify the lesion. In one case the clinical course and the gross pathologic condition of the kidney removed were those of atrophic pyelonephritis, and it was only on microscopic examination of the renal tissue that tuberculosis was discovered.

Bilateral pyelonephritis.—Occasionally a patient is observed with a definite chronic bilateral pyelonephritis with function of one kidney practically normal and that of the other greatly reduced. As a rule, however, the function of both kidneys is reduced symmetrically and surgical treatment is contraindicated. If chronic infection is found in both kidneys and one kidney has become atrophic, the latter should

be removed, providing the function of the other kidney is normal or shows evidence of hypertrophy (Fig. 90).

PATHOLOGY

The kidneys in this series of cases were small, averaging 58 gm. in weight, and from 3 to 5 cm. in their greatest diameter. They were firm and contracted, of much the same consistency as the fibrosed kidneys in arteriosclerosis. The outer surface is usually smooth and rounded instead of deeply scarred and granulated as in chronic nephritis. The



FIG. 91 (Case A298617).—Atrophic pyelonephritis with destruction and fibrosis of most of the kidney substances.

capsule is thickened and strips easily. One half of the kidney may be involved more than the other, and in several cases the infection was apparently confined entirely to one pole, with hypertrophy of the tissue in the remaining portion of the kidney. In one patient a double kidney was found with complete duplication of the pelvis and ureter. The atrophic pyelonephritis was confined entirely to the upper half, the lower half being quite normal. A deposit of fat is sometimes found surrounding the renal pelvis, which is evidently the result of chronic pyelonephritis.

The tissues lining the renal pelvis were greatly thickened, contracted and granular, often showing irregular folds as though shrunk to occupy a smaller space. In a few kidneys the pelvis showed evidence of a slight dilatation, although in the majority it had a capacity of only a few cubic centimeters. The ureters are generally thickened and dilated, especially in the upper third, and the ureteropelvic juncture may be moderately occluded. On section irregular areas of condensed and fibrous tissue are seen. The cortex of the kidney in most cases is

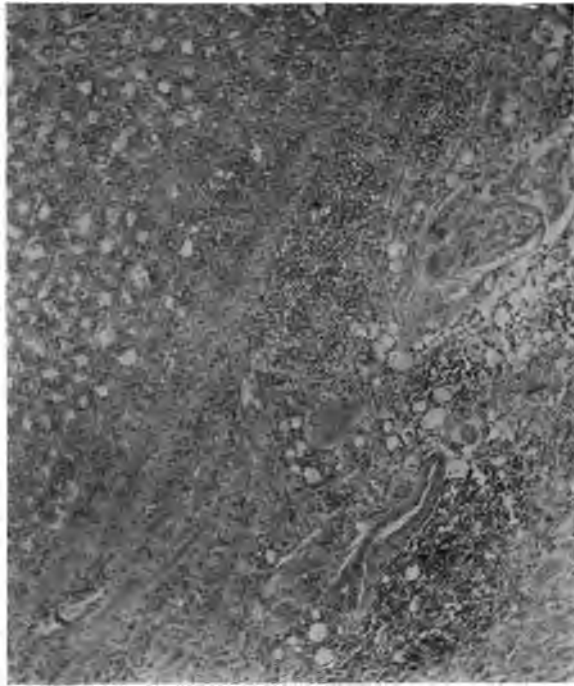


FIG. 92 (Case A142332).—Atrophy and fibrosis with marked round-cell infiltration.

much thinner than normal, at times being only 2 to 3 mm. in depth. Occasionally the fibrosis and destruction of kidney substance were so marked that it was impossible to find the dividing line between the medulla and the cortex. Bands of fibrous tissue and thick walled blood-vessels could be made out readily on the cut surface. Occasionally inflammatory cystic degeneration was found, especially in areas in which cicatricial changes were marked (Fig. 91).

The microscopic examination showed a generalized atrophy of most

of the functioning renal tissues together with a marked increase in the connective-tissue elements. There were marked thickening and sclerosis of practically all the blood vessels. The intima especially was so thickened that at times it completely occluded the lumen of the vessel (Fig. 92).

The tubules in most cases showed a general atrophy; at times there was a decrease in the number or even a complete absence in certain areas. The epithelial cells lining the tubules were flat and compressed. In some sections dilated lumina were found filled with pink staining colloid material, possibly the altered obstructed secretion of the tubular epithelium. Occasionally areas of normal or even hypertrophied tubules and glomeruli were found in close apposition to fields of complete fibrosis. Often areas of atrophied tubules with an excessive number of glomeruli were compressed together in the meshes of interlacing bands of fibrous tissue. This grouping of the glomeruli shows a generalized atrophy of the interstitial elements. The glomeruli, at times merely small hyaline areas, often formed the center of a thick fibrous nodule. In one case a large hyaline mass was found, in the center of which was an extensive area of calcareous degeneration. Infiltration of small round cells was found in all sections. These cells, mononuclear lymphocytes and plasma cells, in some cases were quite extensively distributed, in others they were clumped and grouped, especially around hyalinized and fibrosed areas.

ETIOLOGY

The etiology offers a very interesting problem. It is quite evident that the condition is not the end-result of the usual pyelonephritis. It can hardly be explained by primary stricture of the ureter with hydronephrosis and secondary atrophy since the dilatation of the pelvis is not great enough to cause atrophy, and, furthermore, the atrophy is not symmetric, but is frequently confined to one portion of the kidney. The possibility of a primary stricture of the ureter, with diffuse acute infection in the renal cortex and consequent atrophy, before the hydronephrotic sac is developed, may be considered. In cases of operations for perinephritic abscess or drainage of surgical kidneys it is possible that the renal atrophy was secondary rather than primary.

It seems more probable that the atrophic condition is the result of a primary septic infarct. This is further borne out by the fact that the

atrophy is at times confined to one portion of the kidney. The secondary dilatation of the pelvis and ureter may be explained either by a secondary stricture of the lower ureter or by an inflammatory atonic dilatation. The latter theory is supported by the fact that no evidence of ureteral obstruction is encountered, even by catheters of large caliber introduced into the dilated ureter.

RESULTS OF OPERATION

At operation it is often difficult to find the diseased kidney since it is often displaced and covered with fibrous tissue as a result of accompanying perinephritis. The kidney may be only 3 to 5 cm. in diameter and is easily overlooked. Although the small amount of tissue removed is out of proportion to the severity of the patient's symptoms, nevertheless such symptoms disappear following removal of the kidney.

The results of operation for atrophic pyelonephritis have been very satisfactory. Improvement or cessation of vesical symptoms and improvement of the general condition have been accomplished for practically every patient.

Only three patients reported that evidence of urinary infection persisted, and only one of these claimed that there was no improvement. One patient was reported as having died from cause unknown three months after operation.

A TEST FOR EARLY RENAL INSUFFICIENCY: PRELIMINARY PAPER*

THOMAS B. MAGATH

For the past two decades many attempts have been made to study the renal function of patients who have demonstrable primary lesions of the kidneys, or lesions that affect the kidneys secondarily. As the result of all the methods known, many have claimed that the most generally valuable individual test is the estimate of a single sample of blood urea. Many investigators, however, have tried to find some test that would demonstrate an earlier renal involvement than that which can be shown by an already elevated blood urea. Thus the diagnostic determination of blood uric acid has been developed and it has been shown quite clearly that there may be an elevated blood uric acid in renal involvement long before the blood urea is above normal, because the kidneys excrete uric acid with the greatest difficulty of any known nonprotein substance. The determination of uric acid is of more value than urea in the early diagnosis of nephritis.

In cases in which the blood uric acid is marginal; that is, between 2.5 and 3.5 mg. for each 100 c.c. the question often is raised of whether there is any significance in the results. It was thought possible to answer this question and at the same time demonstrate earlier lesions than could be shown by a single blood uric acid determination, if the patient were tested for his ability to excrete uric acid. Denis showed some years ago that patients with nephritis exhibit an accumulative effect of uric acid in the blood if fed on high purin diets, while normal persons have no change in the blood uric acid under these conditions. Upham and Highley pointed out the necessity of having patients on a constant purin intake in order to study and compare blood uric acid determinations. It seemed logical, therefore, if a patient were fed uric acid and there was a slight lesion of the kidneys too small even to give a very marked rise of blood uric acid with a normal diet, that it might

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be possible to demonstrate an early inability of the kidneys to excrete uric acid and thus determine a possible prenephritic condition. The test was carried out as follows:

The patient was put on a purin-free diet (milk) for three days and the amount of uric acid excreted in the urine was determined for the third twenty-four hours. The method of Folin and Wu was used throughout this work. Three-fourths of the weight of the patient was ascertained and calculated for the weight of body fluids. Enough uric acid was given by mouth to cause a rise in the blood uric acid of about 2.5 mg. for each 100 c.c. if the patient failed to excrete any of it. This usually meant the administration of about 2 gm. of pure uric acid. A determination was then made of the uric acid in the blood. The uric acid excreted during the next twenty-four hours was determined; at the end of this time a second blood uric acid determination was made and compared with that made at the time the drug was administered. It is evident, therefore, that there is a check on any uric acid that might be lost by changes in the rate of absorption in the gastro-intestinal tract.

Three patients were tested in the manner described. None of the three presented blood or urinary findings by the usual methods sufficient to warrant the diagnosis of renal involvement, yet all three had a decided hypertension with practically no other physical findings. In one case the patient excreted, prior to the administration of uric acid, 0.4 gm. in twenty-four hours. At the time he was given uric acid the blood contained 2.5 mg. for each 100 c.c. At the end of the next twenty-four hours the patient had excreted 0.34 gm. of uric acid, and the blood determination showed a concentration of 5.8 mg. for each 100 c.c. Since the other two cases ran parallel, only one will be cited. The patient excreted 0.5 gm. of uric acid in twenty-four hours, prior to the administration of the drug and showed a blood uric acid of 2.8 mg. for each 100 c.c. At the end of twenty-four hours the blood uric acid concentration had not changed and about 70 per cent of the uric acid was recovered in the urine. The first case was interpreted as a prenephritic condition. The other two must, for the present, be considered as essential hypertension without renal involvement.

The uric acid used for these tests was prepared from human urine by the usual method. Several other cases were tested as here outlined; a commercial product of uric acid was used. There was neither rise in the uric acid of the blood nor of the urine, indicating that the failure might be due to the fact that the uric acid was probably not absorbed

in the gastro-intestinal tract, at least not as uric acid. This result is in keeping with observations made by investigators in the past.

Caffein citrate was used in other cases, and here I was able to obtain calculated rises in the blood or urine according to whether the individual was normal or nephritic. From this it would seem that caffein is excreted as uric acid or piles up as uric acid in the blood in cases of nephritis or else some other substance is formed that gives a blue color by the Folin and Wu method. The dose used was about 1 gm. of caffein citrate in capsules at three one-hour intervals just prior to the ingestion of a meal.

The method by which caffein is excreted is still a question of controversy. Sollmann asserts that it is completely and readily absorbed, that very little is excreted as such, and that from 10 to 40 per cent of the substance loses its methyl groups and is excreted as dimethylxanthin or monomethylxanthin; up to 80 per cent is excreted as urea, practically none as uric acid. Cushny asserts that the uric acid of the urine is not increased by the ingestion of caffein. On the other hand, Greene believes that caffein is demethylated in the body and forms xanthin which is excreted in the manner in which any animal xanthin is excreted, namely, as uric acid. Schittenhelm found that feeding caffein increases the amount of uric acid in the urine. Taylor concluded that coffee added to the diet increases the output of uric acid quite markedly, and explained it on the basis of the caffein in the coffee. Benedict repeated, to some extent, the work of Taylor and concluded that caffein at least when ingested as coffee increased the output of uric acid in the urine.

This caffein test has been used in a number of cases which were studied clinically and diagnosed in relation to the condition of the kidney. The cases were divided into three groups, those without lesions of the kidney, those with questionable lesions from a clinical study, and those with definite lesions clinically. The results are shown in Tables 1, 2, and 3. It may be seen that in general the caffein test checked very nicely the clinical findings. Three patients (Table 1) are marked exceptions to this statement. All were on intensive syphilitic treatment and it is possible that they had very slight kidney lesions, which must be quite common with intensive treatment with mercury and arsenic, but cannot be detected clinically. One other exception to the clinical findings is seen in Table 3. A man with a left pyelonephritis had a free output of uric acid, which may be explained on the basis of a competent right kidney. A case diagnosed mild nephritis

TABLE 1
NO LESIONS OF THE KIDNEY

Case.	Diagnosis of nephritis (Conner).	Blood uric acid 1.	Blood uric acid 2.	Difference between 1 and 2.	Urine uric acid 1.	Urine uric acid 2.	Difference between 1 and 2.	Remarks.
A325661	Syphilis.	3.4	3.4	±0.0	0.47	0.69	+0.22	
A343023	Neurosis, migraine, syphilis.	1.3	3.1	+1.8	0.41	0.40	-0.01	Treatment for syphilis.
A342157	Pulmonary tuberculosis.	3.2	2.4	-0.8	0.25	0.86	+0.61	0.4 gm. caffein.*
A342901	Bronchial asthma, prolapse of ovaries.	2.1	1.9	-0.2	0.31	0.37	+0.06	
A341589	Artificial vagina.	2.0	2.8	+0.8	0.15	0.27	+0.12	
A340455	Epilepsy, central nervous system syphilis.	2.5	2.9	+0.4	0.29	0.38	+0.09	Treatment for syphilis.
A342960	Leukorrhea.	1.8	2.0	+0.2	0.38	0.62	+0.24	
A342204	Metrorrhagia, neurosis.	2.3	1.9	-0.4	0.19	0.81	+0.62	
A341076	Chronic sinusitis.	2.4	1.7	-0.7	0.68	0.89	+0.21	
A316534	Central nervous system syphilis, cystitis.	2.3	3.3	+1.0	0.76	0.62	-0.14	Treatment for syphilis.
A340982	Diarrhea, pancreatitis.	2.0	2.2	+0.2	0.40	0.42	+0.02	

* Full dose 0.8 gm. caffein.

TABLE 2

LESIONS OF THE KIDNEY (?)

Case.	Clinical diagnosis (other than renal).	Renal diagnosis.	Blood uric acid 1.	Blood uric acid 2.	Difference between 1 and 2.	Urine uric acid 1.	Urine uric acid 2.	Difference between 1 and 2.	Remarks.
A341014	Hypertrophy of prostate.	Probably slight nephritis.	3.1	2.3	-0.8	0.60	0.77	+0.17	Twelve-hour specimen urine. 0.4 gm. caffeine.* Eighteen-hour specimen urine.
A343173	Exophthalmic goiter.	Probably mild chronic nephritis with arteriosclerosis.	3.8	3.2	-0.6	0.73	0.51	-0.22	
A342739	Pericarditis.	Possibly mild pyelonephritis.	1.7	1.9	+0.2	0.30	0.25	-0.05	
A342897	Bronchial asthma.	Probably mild nephritis.	3.0	2.8	-0.2	0.58	0.58	±0.00	
A340069	Myocarditis.	Possibly nephritis.	3.0	3.0	±0.0	0.56	0.54	-0.02	Twelve-hour specimen urine. 0.4 gm. caffeine.* Eighteen-hour specimen urine.
A341588	Chronic constipation; psychoneurosis.	Possibly mild nephritis.	1.4	2.5	+1.1	0.63	0.74	+0.11	
A224717	Dental infection, nervousness.	No lesion of the kidney (?).	1.4	1.7	+0.3	0.28	0.50	+0.22	
A342605	Anemia, gastritis.	Probably mild nephritis.	1.4	1.8	+0.4	0.28	0.32	+0.04	
A340597	Hernia.	No lesion of the kidney (?).	2.4	3.1	+0.7	0.19	0.46	+0.27	Twelve-hour specimen urine. 0.4 gm. caffeine.* Eighteen-hour specimen urine.
A338792	Hypertension.	Probably some chronic nephritis.	2.6	3.3	+0.7	0.55	0.46	-0.09	
A433090	Achylia gastrica, pyorrhea.	Possibly mild chronic nephritis.	3.6	3.8	+0.2	0.67	0.42	-0.25	

* Full dose 0.8 gm. caffeine.

TABLE 3
DEFINITE LESION OF THE KIDNEY (CLINICALLY)

Case.	General diagnosis (Conner).	Blood uric acid 1.	Blood uric acid 2.	Difference between 1 and 2.	Urine uric acid 1.	Urine uric acid 2.	Difference between 1 and 2.	Remarks.
A338961	Chronic nephritis, arteriosclerosis.	2.0	2.8	+0.8	0.42	0.29	-0.13	0.4 gm. caffeine,* eighteen-hour specimen of urine.
A342561	Left pyelonephritis with chronic nephritis.	3.8	3.3	-0.5	0.70	0.99	+0.29	
A341707	Hydronephrosis with stones, nephritis.	1.9	2.5	+0.6	0.26	0.39	+0.13	
A340546	Infected hydronephrosis.	2.4	3.1	+0.7	0.13	0.42	+0.19	
A341889	Mild nephritis, arteriosclerosis, hypertension.	3.0	3.5	+0.5	0.83	1.00	+0.17	
A339900	Mild nephritis.	2.2	3.0	+0.8	0.26	0.26	+0.02	
A341021	Mild chronic nephritis, hypertension, arteriosclerosis.	2.1	2.8	+0.7	0.90	0.81	-0.09	
A342111	Chronic nephritis, hypertension.	3.4	3.8	+0.4	0.43	0.40	-0.03	
A342499	Nephritis, arteriosclerosis, hypertension.	1.6	2.7	+1.1	0.77	0.54	-0.23	
A343063	Chronic nephritis.	3.7	3.7	=0.0	0.39	0.53	-0.14	0.4 gm. caffeine.*
A338719	Mild nephritis.	3.2	2.8	-0.4	0.44	0.48	-0.04	Gout (?).
A341339	Chronic nephritis, hypertension.	2.8	2.8	=0.0	0.37	0.65	+0.18	0.4 gm. caffeine.*
A340860	Mild nephritis.	2.4	2.2	-0.2	0.37	0.98	+0.61	
A341816	Chronic nephritis.	2.5	2.8	+0.3	0.70	0.42	-0.28	Eighteen-hour specimen urine.
A342234	Right kidney infected.	2.0	2.4	+0.4	0.52	0.68	+0.16	
A343473	Mild nephritis.	3.2	3.9	+0.7	0.62	0.36	-0.26	Eighteen-hour specimen urine.

* Full dose 0.8 gm. caffeine.

with some question of gout showed practically no increase in the output of uric acid, but rather a little diminution in the second blood specimen taken. This finding is interesting in view of the fact that uric acid is believed by some observers to be retained in the tissues in cases of gout.

Recently MacLean and de Wesselow have used a urea concentration test showing that earlier renal involvements may be demonstrated than by a simple blood urea estimation. The test consists, briefly, in feeding the patient 15 gm. of urea and determining the amount excreted in the urine in two hours' time. It remains to be seen whether this test furnishes more information than a single uric acid determination, and certainly from a theoretical standpoint it could not show as early a renal involvement as the proposed uric acid concentration test outlined in this paper. These tests were performed many months before the publication of the work of MacLean and de Wesselow, in an attempt to demonstrate the rôle of renal insufficiency in essential or idiopathic hypertension. The pressure of other investigations, however, has made it impossible to carry on the work at the present time and this note is published in the hope that others interested in such cases will give the test a trial and will perhaps obtain a series that may be compared with other renal functional tests.

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BENCE-JONES PROTEINURIA—A REPORT OF THREE CASES WITH METABOLIC STUDIES*

WALTMAN WALTERS

In 1847, Henry Bence-Jones reported before the Royal Society of London the finding of a peculiar form of protein in the urine in a case of osteomalacia fragilis rubra; the most characteristic feature of this protein was its behavior toward nitric acid. This reagent yielded a precipitate with the urine of the patient which dissolved on heating and reappeared on cooling, a reaction which led Bence-Jones to believe that it was not the ordinary serum albumin of nephritis. The kidneys were sound clinically. At necropsy the ribs were cut with the greatest ease and the bodies of the vertebræ were capable of being sliced with a knife. Microscopically the kidneys were normal.

Thirty-nine years passed before a second case was reported by Kühne, who published the result of a urinalysis in which he rediscovered the reactions of Bence-Jones, and a diagnosis of osteomalacia was made clinically, but necropsy was not obtained.

Kahler, in 1889, described a third case in which the diagnosis also was osteomalacia since the urine gave Bence-Jones reactions, but at necropsy instead of osteomalacia, multiple round-cell sarcoma, that is, multiple myeloma, was disclosed. Kahler suggested that Bence-Jones reactions might be of service in the diagnosis of multiple myeloma and that possibly the other two cases of osteomalacia with proteinuria had been instances of this disease.

From 1889 to 1917, 205 instances of Bence-Jones proteinuria have been reported, the greatest number being in cases of multiple myeloma. A summary and complete bibliography of the subject up to 1917 is contained in Rosenbloom's paper. According to Miller and Baetjer 80 per cent of all patients with myeloma have Bence-Jones protein in the urine. During the last twenty years numerous cases have been reported of the existence of this protein in other diseases (Table 1). Bence-Jones proteinuria, therefore, is not essentially dependent on one

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TABLE 1
OCCURRENCE OF BENCE-JONES PROTEINURIA IN VARIOUS DISEASES

	Cases.
Multiple myeloma	80 per cent of cases.
Lymphatic leukemia	3 cases (Askanzy, Decostello).
Myeloid leukemia	3 cases (Boggs).
	1 case (Miller-Baetjer).
Myxedema	1 case (Fitz).
Basedow's disease	1 case (Von Jaksch).
Carcinomatosis	1 case, primary carcinoma of stomach (Orum).
Nephritis	2 cases (Miller and Baetjer).
	1 case, only instance of Bence-Jones proteinuria observed in a case of genuine nephritis; no bone lesions other than those of secondary anemia (Coat and Brewer).
Hypertension	5 cases, no albumin, but casts (Miller and Baetjer).
Pyrodin poisoning	Experimentally produced in dogs.

disease, but is a manifestation of disease affecting endogenous metabolism.

On the whole, the most characteristic reactions of Bence-Jones protein are its precipitation from acid urine at temperatures of from 55 to 60 C., its disappearance at the boiling point with the formation of a clear solution, and its reappearance as the solution cools. When concentrated nitric or hydrochloric acid is added to urine containing Bence-Jones protein the latter precipitates in a dense white cloud which goes into solution as the temperature is raised to the boiling-point and reappears again as the urine is cooled.

The origin of this protein is still in doubt; the most tenable hypothesis, that of Hopkins and Savory, is that it represents either normal, abnormal, or aberrant stages of bone synthesis, the completion of which is hindered by indeterminate pathologic conditions.

Three cases of Bence-Jones proteinuria are herewith reported: one in a patient with an obscure diagnosis, one in a patient with a generalized carcinomatosis, and one in a patient with true multiple myeloma. Metabolic studies were made on each patient to determine variations in excretion on various diets. The quantitative estimation of Bence-Jones protein in each specimen of urine was determined by the method of Folin and Denis, with the exception that the urine was kept at a constant temperature of 60 C. for three hours instead of for twelve hours.

REPORT OF CASES

Case 1 (A319680). Mr. H. M. R., aged forty-one years, registered in the Mayo Clinic September 24, 1920. At various intervals for the past three years considerable amounts

TABLE 2
EXCRETION OF BENGE-JONES PROTEIN DURING THREE-HOUR INTERVALS IN CASE 1

Hours.	General diet.											
	8/31/20 to 9/1/20		9/1/20 to 9/2/20		9/2/20 to 9/3/20		9/3/20 to 9/4/20		9/4/20 to 9/5/20		9/5/20 to 9/6/20	
	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.
8 p.m. to 8 a.m.	1,455	10.45	640	6.46	1,150	8.72	1,150	8.36	1,050	8.19	675	2.39
8 a.m. to 11 a.m.	298	2.02	360	2.38	95	2.10	210	1.21	460	6.51	325	2.93
11 a.m. to 2 p.m.	350	2.48	375	1.89	120	2.13	250	2.31	400	2.30	300	2.12
2 p.m. to 5 p.m.	230	2.61	240	2.07	128	2.30	165	2.56	175	0.65	170	3.61
5 p.m. to 8 p.m.	139	1.34	505	2.24	161	5.21	250	2.54	135	5.05	180	1.72
Total.....	2,432	18.88	1,910	15.04	2,036	20.36	2,025	16.68	2,280	22.68	1,450	10.86
Total night.....		10.45		6.46		8.72		8.36		8.19		2.93
Total day.....		8.43		9.58		11.64		8.32		14.49		8.47
Hours.	Nonprotein diet.											
	9/9 to 9/10		9/10 to 9/11		9/11 to 9/12		9/12 to 9/13		9/13 to 9/14		9/14 to 9/15	
	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.
8 p.m. to 8 a.m.	810	8.19	910	7.33	750	7.56	1,310	6.73	840	6.73	895	5.83
8 a.m. to 11 a.m.	50	0.98	940	1.98	905	1.73	190	1.92	150	2.11	75	2.13
11 a.m. to 2 p.m.	178	2.71	880	2.20	735	1.94	130	2.54	130	2.11	130	2.11
2 p.m. to 5 p.m.	920	2.83	940	2.13	450	2.93	1,540	1.54	1,190	2.08	160	2.13
5 p.m. to 8 p.m.	190	2.33	140	1.50	880	2.10	245	2.43	130	2.08	130	2.08
Total.....	1,478	16.55	1,810	15.15	1,810	15.60	3,925	28.13	1,440	14.54	1,370	14.38
Total night.....		8.19		7.33		7.56		6.73		6.73		5.83
Total day.....		8.36		7.81		8.04		7.98		7.81		8.43
Hours.	High protein diet.											
	9/16 to 9/17		9/17 to 9/18		9/18 to 9/19		9/19 to 9/20		9/20 to 9/21		9/21 to 9/22	
	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.
8 p.m. to 8 a.m.	890	6.54	900	6.54	890	6.54	890	6.54	890	6.54	890	6.54
8 a.m. to 11 a.m.	300	2.03	300	2.03	300	2.03	300	2.03	300	2.03	300	2.03
11 a.m. to 2 p.m.	215	2.15	215	2.15	215	2.15	215	2.15	215	2.15	215	2.15
2 p.m. to 5 p.m.	310	1.96	310	1.96	310	1.96	310	1.96	310	1.96	310	1.96
5 p.m. to 8 p.m.	190	2.75	190	2.75	190	2.75	190	2.75	190	2.75	190	2.75
Total.....	1,835	15.86	1,735	15.86	1,835	15.86	1,835	15.86	1,835	15.86	1,835	15.86
Total night.....		6.54		6.54		6.54		6.54		6.54		6.54
Total day.....		9.32		9.32		9.32		9.32		9.32		9.32

of albumin had been found in his urine. In June, 1919, he had had an acute attack supposed to be referable to the gallbladder which was followed by a complaint in some respects suggestive of duodenal ulcer. Pallor of skin and weakness were increasing.

On examination the patient's blood pressure was found to be normal. The urine contained albumin, but was free from casts, pus cells, or red blood corpuscles. The values for blood urea, total nonprotein nitrogen, and for the phenolsulphonephthalein functional test were normal. Because of the presence of large quantities of albumin in the presence of these normal findings Bence-Jones proteinuria was suspected in spite of the absence of growths or pains in the bones, and the protein was then found in considerable quantities (Table 2). An additional feature of interest was the absence of a demonstrable pathologic lesion of any of the bones, either by physical examination or by roentgenographic studies. A roentgenogram of the gastro-intestinal tract disclosed nothing abnormal and an exploratory operation revealed a normal stomach and a normal gallbladder. Specimens from the pancreas and from the liver revealed mild chronic inflammatory changes.

Case 2 (A333896). Mr. J. E. D., aged forty-nine years, came to the Clinic September 14, 1920. He stated that the mass which had been on the right side of the chest for many years had increased in size during the last six months and that it had become somewhat tender. In June, 1920, during a sudden twist of his body, he fractured the tenth rib on the right side in the posterior axillary line. He had had pain for one month in the lower portion of the right chest, a cough, and a dull aching pain across the lumbar and sacral vertebrae.

The outstanding features on physical examination were two tumor masses, one approximately 4 cm. in diameter, attached to the tenth right rib in the anterior axillary line, one approximately 2.5 cm. in diameter attached to the fourth left rib in the parasternal line. On fluoroscopic examination there was evidence of infiltration of both lungs which showed many nodular areas of metastasis characteristic of carcinoma. Metastasis was also found in the lumbar and sacral vertebrae. The primary origin of the carcinoma was not discovered. Bence-Jones proteinuria was discovered early in this case (Table 3).

TABLE 3

EXCRETION OF BENCE-JONES PROTEIN DURING THREE-HOUR INTERVALS IN CASE 2

Hours.	General diet.					
	9/19/20 to 9/19/20		9/19/20 to 9/20/20		9/20/20 to 9/21/20	
	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.	Urine, c.c.	Protein, gm.
8 p.m. to 8 a.m.....	1,375	1.02	860	1.33	450	4.9
8 a.m. to 11 a.m.....	385	0.25	320	0.70	219	0.47
11 a.m. to 2 p.m.....	160	0.15	350	0.77	186	0.46
2 p.m. to 5 p.m.....	255	0.32			35	0.07
5 p.m. to 8 p.m.....	340	0.51	310	0.88	218	0.26
Total.....	2,515	2.25	1,840	3.68	1,108	6.16
Total night.....		1.02		1.33		4.9
Total day.....		1.23		2.35		1.26



FIG. 93 (Case 3).—Tumor mass of left thoracic wall, and kyphosis of the dorsal vertebrae.

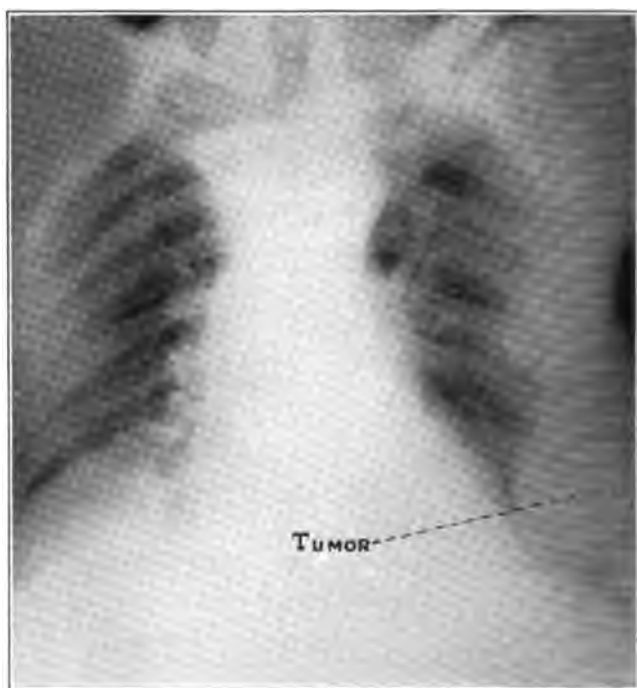


FIG. 94 (Case 3).—Tumor mass of the left thoracic wall.

Case 3 (A339622). Mr. R. L., aged sixty-nine years, examined in the Clinic November 15, 1920, had been well until two years before, when stiffness of the neck and back had developed following exposure and a wetting. Four months later a nodule was discovered on the left thoracic wall attached to the fifth and sixth ribs; it began to increase in size and became quite painful. The patient complained of extreme pain in the right half of the thorax and a troublesome loose productive cough.

Repeated examinations of the lungs were negative. The tumor was attached to the fifth and sixth ribs and in the left anterior axillary line measured 10 by 7.5 cm. The lower portion of both sides of the thorax bulged and the dorsal vertebræ were fixed (Figs. 93 and 94). There was a marked tenderness to pressure on the second, third, fourth,



FIG. 95 (Case 3).—Multiple myeloma in bones of the skull. The dark areas are areas of destruction of bone. The increased thickness of the skull, especially in the occipital region, is suggestive of Paget's disease of the bone, but is distinguished from it because the dark areas represent bone destruction, while with Paget's disease there are areas of bone production or eburnation.

fifth, and sixth ribs of the right side in the parasternal and anterior axillary lines. The skull and the long bones were not tender to pressure.

A roentgenogram of the bones showed multiple circumscribed areas of destruction, varying in size from 0.2 to 0.5 cm., in the skull, the femurs, tibiae, and radii, and a fracture of the fifth, sixth, seventh, and eighth ribs of the right side (Figs. 94-96).

A specimen removed from the tumor mass on the left side of the chest wall was reported to be round-cell sarcoma or myeloma.

In this case and in Case 1 a large amount of albumin in otherwise negative urine, a severe secondary anemia, normal blood pressure, and

normal kidney function suggested Bence-Jones protein which was found to constitute the entire albumin content (Table 4).

According to Hamburger's classification there are three types of multiple myeloma, (1) multiple myeloma mistaken for osteomalacia (Kahler's case); (2) visible tumors with pathologic fractures, and (3)



FIG. 96 (Case 3).—Multiple myeloma in the radius and ulna. The dark, blotchy areas show destruction of bone.

multiple myelomas with vague or absent bone symptoms, diagnosis being made at necropsy. Case 1 probably belongs to the latter group and in many respects is similar to the case reported by Ellinger, whose patient too had symptoms of gallbladder disease with jaundice, chills, and fever for six weeks, a marked progressive secondary anemia, a Bence-Jones proteinuria, and no symptoms referable to the bones.

The urine in Case 1, after standing for three days under toluol, became darker and deposited a large amount of white material at the

TABLE 4

EXCRETION OF BENCE-JONES PROTEIN DURING TWELVE-HOUR INTERVALS IN CASE 3

	Total nitrogen, gm.	Protein, gm.	Diet.
11/9/20 8 a.m. to 8 p.m.....	2.4	5.4	Milk.
8 p.m. to 8 a.m.....	6.3	8.45	
11/10/20 8 a.m. to 8 p.m.....	5.0	7.8	Milk.
8 p.m. to 8 a.m.....	2.0	4.79	
11/11/20 8 a.m. to 8 p.m.....	3.3	7.4	Milk.
8 p.m. to 8 a.m.....	4.4	7.3	
11/12/20 8 a.m. to 8 p.m.....	3.0	6.9	General.
8 p.m. to 8 a.m.....	3.8	9.44	
11/13/20 8 a.m. to 8 p.m.....	—	—	—
8 p.m. to 8 a.m.....	—	—	—
11/14/20 8 a.m. to 8 p.m.....	1.7	10.5	Mosenthal.
8 p.m. to 8 a.m.....	1.5	3.87	
11/15/20 8 a.m. to 8 p.m.....	3.8	9.3	General.
8 p.m. to 8 a.m.....	2.2	5.7	
11/16/20 8 a.m. to 8 p.m.....	2.0	9.1	General.
8 p.m. to 8 a.m.....	2.0	5.76	
11/17/20 8 a.m. to 8 p.m.....	2.4	2.4	General.
8 p.m. to 8 a.m.....	4.4	8.25	
11/18/20 8 a.m. to 8 p.m.....	—	—	General.
8 p.m. to 8 a.m.....	3.7	6.67	
11/19/20 8 a.m. to 8 p.m.....	3.9	7.0	Starvation.
8 p.m. to 8 a.m.....	2.7	5.07	
11/20/20 8 a.m. to 8 p.m.....	—	—	—
8 p.m. to 8 a.m.....	—	—	—
11/21/20 8 a.m. to 8 p.m.....	2.7	5.73	General.
8 p.m. to 8 a.m.....	3.2	7.07	
11/22/20 8 a.m. to 8 p.m.....	6.3	18.5	General.
8 p.m. to 8 a.m.....	3.0	2.34	
11/23/20 8 a.m. to 8 p.m.....	4.7	6.04	General.
8 p.m. to 8 a.m.....	5.2	6.04	

bottom of the container. When shaken the urine exhibited a sheen resembling that of castile soap and revealed under the microscope the typical crystals of Bence-Jones protein (Fig. 97). These crystals had



FIG. 97 (Case 1).—Bence-Jones crystals, which precipitated spontaneously from urine at room temperature.



FIG. 98 (Case 1).—Bence-Jones crystals, which precipitated spontaneously from urine at room temperature.

precipitated spontaneously at room temperature; the only other instance of spontaneous precipitation is recorded by Rosenbloom. Mag-

nus-Levy, Grutternick, and de Graef succeeded in precipitating Bence-Jones protein in crystalline form. Dr. D. W. Wilson, of Johns Hopkins Medical School, working on this case with us, succeeded in isolating the protein from the blood plasma.

Blood examinations in our cases and in those of Anders and Boston showed a marked secondary anemia (Table 5).

TABLE 5
BLOOD ANALYSIS IN THREE CASES OF BENCE-JONES PROTEINURIA

	Case 1.						Case 2.	Case 3.
	7/21/20.	7/29/20.	8/4/20.	9/1/20.	9/10/20.	9/17/20.	9/19/20.	9/9/20.
Hemoglobin	45.0	40.0	45.0	44.0	40.0	40.0	50.0	61.0
Erythrocytes (millions)	2.5	2.84	2.49	3.01	2.55	2.7	3.56	3.27
Leukocytes	3,200	3,600	2,800	5,800	3,400	5,000	5,600	11,600
Color index	0.9	0.7				1.7+	0.7+	0.7+
Cells counted	200	200	200	200	200	200	200	500
Polymorphonuclear								
neutrophils	45.0	48.0	40.5	64.5	62.5	41.0	68.0	78.0
small lymphocytes	2.5	46.0	57.0	32.0	31.0	51.0	15.0	16.0
large lymphocytes	0.5	5.5	2.5	2.5	6.0	2.5	5.0	4.8
monocytes	1.0	0.5				2.0	1.5	1.0
Basophils				1.0	0.5	2.5		
Anisocytosis	Slight	Moderate	Slight			Moderate		Slight
Poikilocytosis	Slight	Slight	Slight			Moderate		Slight
							Monocytes 10.5	

EXPERIMENTAL STUDY

Effect of diet on output of Bence-Jones protein.—The problem was to ascertain the effect of food, particularly of protein intake, on the quantitative output of Bence-Jones protein. Accordingly the patients were placed on various diets and the urine was collected at three-hour intervals during the day and during the twelve-hour period from 8 p.m. to 8 a.m. The amount of protein in each specimen was determined by Folin and Denis' method with modifications. A similar problem was studied by Hopkins and Savory, in 1911, and by Folin and Denis, in 1914. These investigators found no definite or constant relation between total nitrogen and the albumin in the urine, and that the protein content of food bears no direct relation to the elimination of Bence-Jones protein.

In this series the first patient excreted from 10.8 to 22.68 gm. of Bence-Jones protein every twenty-four hours whether on a general diet, on a low protein diet, or on a high protein diet (Table 2). The second patient remained under observation only three days, and since

he was somewhat stuporous, collections of urine were not accurate (Table 3). In both cases, however, the amount excreted during the day was in most instances somewhat in excess of that excreted during the night; on some days the reverse was true. The amounts excreted during three-hour periods remained practically constant. The specimens of urine from the third patient were collected during the day and night (Table 4). Estimations of the total urinary nitrogen as well as of the quantity of Bence-Jones protein were made by means of the micro method of Folin. There was little constant variation in the amount of Bence-Jones protein excreted by the three patients irrespective of protein intake; and there is not a constant relation between the quantity of Bence-Jones protein and the total nitrogen excreted.

Effect of intravenous injection of Bence-Jones protein.—In order to determine the effect of an intravenous injection of the protein 1.6 gm. of Bence-Jones protein in 20 c.c. of normal salt solution was injected intravenously at 8.25 p.m. November 22, 1920. The patient began to chill at 9.15 p.m. and continued to do so until 11 p.m. The twelve-hour specimen of urine from 8 p.m. to 8 a.m. contained 2.34 gm. of Bence-Jones protein, with a total nitrogen of 3.01 gm. Twelve hours later the quantity of Bence-Jones protein increased to 18.5 gm., with a total nitrogen of 6.26 gm. These values were the highest obtained at any time from this patient.

Studies of saliva, bronchial secretions, and cerebrospinal fluid.—November 18, 1920 saliva and bronchial secretion in Case 2 were examined for Bence-Jones protein since the patient had had a productive cough for many days. A few drops of acetic acid (2 per cent) were added to the saliva; mucin was precipitated and filtered out. The filtrate was heated and a white precipitate (turbidity) appeared which did not change when the solution reached boiling-point. A precipitate was not obtained when saturated ammonium sulfate was added to the saliva. Bence-Jones protein was therefore absent.

A few drops of nitric acid (concentrated) were added to the material coughed up by the patient; the white precipitate was filtered off. The filtrate heated to the boiling-point gave a clear solution, which when cooled became quite turbid and cleared again when it was boiled. This was positive evidence of Bence-Jones protein in the bronchial secretion. The spinal fluid was examined for Bence-Jones protein, but none was found.

CONCLUSIONS

1. A large quantity of albumin in otherwise negative urine in a patient with normal renal function and normal blood pressure and a marked secondary anemia should suggest the possibility of Bence-Jones proteinuria, especially when bone lesions are present.

2. Bence-Jones proteinuria is significant from a diagnostic and from a prognostic standpoint of multiple myeloma, since it occurs in 80 per cent of all cases and usually is followed by death within two years.

3. The quantity of Bence-Jones protein excreted is independent of the protein intake, evidenced by an approximately constant excretion for three-hour periods, irrespective of changes in diet.

4. The amount of Bence-Jones protein excreted during the night when food is not taken is only slightly less than the amount excreted during the day.

5. There is not a constant relationship between the quantity of Bence-Jones protein and the total urinary nitrogen excreted.

6. As the finding of Bence-Jones protein in the urine led to its detection in the blood, it may be possible that other proteins of a similar or dissimilar nature are in existence in the blood and are not excreted by the kidneys.

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THE SIGNIFICANCE OF SLIGHT ALBUMINURIA*

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Slight albuminuria in itself has no clinical significance. This statement in effect may be found in standard text books of medicine or of clinical laboratory methods, and it would be the answer of any clinician if he were asked what significance he attached to the finding of a slight amount of albumin in a single passed specimen of urine. Why, then, should the matter be the subject of discussion before a convention of medical directors of life insurance companies where statistical evidence regarding life expectancy is of paramount interest? Why is urinalysis considered of any importance by men interested in general medicine?

The statement regarding the different viewpoints of the clinician and of the life insurance examiner is as trite as that regarding the value of the demonstration of albuminuria. The reason for the difference of opinion is that the life insurance examiner must assert that the person examined is free from physical impairment at the time of examination, the applicant realizing that the time must come when he will succumb to disease and reap the benefit of his thrift from the insurance company, while the clinician examines a person supposedly sick, who shares the hope with the physician that any pathologic condition found may be corrected.

One of the most popular questions for debate, if one is to judge from the mass of material that has been written on the subject, is the manner in which urine should be examined for the presence of albumin. Usually in the urinalysis report the statement is made that a test shows a very slight trace, a trace of albumin, or various larger amounts as the case may be. At the Mayo Clinic it has been the rule for years to report albuminuria on a scale of 0, 1, 2, 3, 4, according to the judgment of the technician. In spite of the massed evidence that has been published on this subject there is still need for methods of evalu-

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ating the significance of albuminuria, and great need of standardizing a method for reporting roughly the quantity of albumin.

In the preparation of this paper we considered several lines of approach. It might at first seem that the most obvious method would be to study a large series of cases from the records of our Clinic from the standpoint of significance of albuminuria in diagnosis. It might also be supposed that the study of massed statistics in any clinic would hold some valuable evidence with regard to prognosis in cases of slight albuminuria. It is impracticable to gain much evidence from statistical studies of this kind, however, for a clinician must ever return to the dictum that slight albuminuria in itself is of no significance. It was then decided to study the significance of albuminuria in the daily routine of the Mayo Clinic from the viewpoint of the life insurance examiner. First, an investigation was undertaken on methods for testing albumin; second, a series of cases was especially studied clinically, and third, the type of functional tests that might be added to the life insurance examination was considered.

COMPARATIVE TESTS FOR ALBUMIN

The routine method of testing for albumin in our laboratory is that used chiefly by life insurance examiners, namely, heat and acetic acid. The top layer of urine in the test tube is boiled briskly, to which 10 per cent acetic acid is added and the urine again boiled; cloudiness indicates the presence of albumin, which is estimated on a scale of 0, 1, 2, 3, 4. Variations of this test are well known, such as the use of brine, or the acidulating of the urine before heating in order to render the test more sensitive. Heller's test (cold nitric acid), while it is known not to be very sensitive to small quantities of albumin, is a standard control test. A new test reported by Stewart two years ago was tried with interest. His reagent consisted of picric acid 10 gm., magnesium sulfate 400 gm., citric acid 20 gm., and water 1500 c.c. This reagent is practically the Esbach reagent with its specific gravity increased by magnesium sulfate. Centrifuged urine is stratified on the reagent as in any of the usual methods. The presence of albumin is noted by the usual ring formation. Stewart claims that it is accurate and far more sensitive than Heller's test. In connection with this test, it seems scarcely necessary to refer to Tsuchiya's phosphotungstic acid reagent as being more reliable than the Esbach reagent in carrying out the ordinary sedimentation method for the quantitative deter-

mination of albumin. In passing, Tanret's solution and Spiegler's reagent may be mentioned as substances that have been used especially for the detection of minute amounts of albumin. The last reagent that we care to mention is sulfosalicylic acid, because, in the opinion of many, this is a most valuable substance for the detection of slight quantities of albumin, and because it was used as a test substance in our comparative study.

In the course of the daily routine urinalysis four of these reagents—heat and acetic acid, Stewart's picric acid reagent, sulfosalicylic acid, and cold nitric acid—were used by four different persons in testing for albumin. The total number of samples of urine examined was set at 100, simply for the convenience of speaking in terms of percentage. The conditions of the tests were always uniform, as the same four persons always carried out the procedures. In Table 1 are shown the results of the comparison of these four tests. In Table 2 the results

TABLE 2
A COMPARISON OF TESTS FOR ALBUMIN
(100 Specimens of Urine)

Heat and acetic acid.	Stewart's test.	Sulfosalicylic acid.	Instances of agreement, per cent.
+	+	+	33
+	+	0	6
+	0	+	0
0	+	+	5
+	0	0	8
0	+	0	3
0	0	+	1
0	0	0	44

are summarized without regard to the degree of albuminuria. Heller's cold nitric acid test was positive only seven times in the entire series of 100 examinations, although albumin was reported, by some method, in 56 per cent of the samples. The three more sensitive tests only are compared; in 33 per cent of the total number albumin was detected by all three methods. The results from Stewart's test and from heat and acetic acid were positive in 6 per cent, in which no albumin was detected by means of sulfosalicylic acid. In 5 per cent Stewart's test and the sulfosalicylic acid test were positive when the heat and acetic acid test was negative. In 8 per cent the heat and acetic acid test was the only one reported to be positive; in 3 per cent Stewart's test alone

was positive; and in one instance sulfosalicylic acid was positive when the other tests were negative.

TABLE 3
RELATION OF CASTS, BLOOD, AND PUS TO ALBUMIN
(100 Specimens of Urine)

Test.	Albumin.	Casts, per cent.	Blood, per cent.	Pus, per cent.	Microscopic negative, per cent.
Heat and acetic acid.....	48	20	19	94	2
Stewart's reagent.....	48	15	19	88	4
Sulfosalicylic acid.....	40	15	22	92	2
Heller (nitric acid).....	7	14	43	86	0
Total positive albumin (all tests)...	56	25	16	96	4
Negative albumin.....	44	9	0	28	50

Table 3 shows the relation of microscopic findings to the albumin in this series of tests. Pus in the urine is reported on a scale of 1, 2, 3, 4, the number of cells in the field of a 4 mm. objective being counted. Up to twenty cells in each field the count is graded 1, from twenty to fifty pus cells is graded 2, an estimation of from fifty to 200 cells is graded 3, and a field packed full of cells, or more than 200, is graded 4. Various grades of pus, usually the first degree, were found in 94 per cent of the specimens that were positive for albumin with heat and acetic acid; 88 per cent with Stewart's test, 92 per cent with sulfosalicylic acid, and in 86 per cent with nitric acid. The total number of positive reactions with any test was 96 per cent. Twenty-eight per cent of the specimens negative for albumin were reported to contain pus. Reference to Table 3 will also bring out the fact that red blood cells were reported in 16 per cent of all the specimens of urine positive for albumin by some test. There was no discrepancy in those findings, as the three sensitive tests agreed in every instance in which red blood cells were found microscopically. The comparative percentages of casts are shown to be slightly in favor of Heller's test, as casts were found in 20 per cent of specimens tested by this method, and slightly less in the other tests. It was interesting also to note that in four instances (9 per cent) the urine specimens reported to be negative by all methods for albumin contained hyaline casts.

Criticism would certainly be just with regard to the relative merits of tests for albumin in this short series. The impression, however, seems to be justified that apparently there is a relation between the

finding of pus microscopically and the finding of albumin in the urine. This in a urinalysis on a passed specimen might be misleading, if deductions were attempted with regard to the relation of albuminuria to a pathologic condition in the kidney, for it is needless to say that the pus might be coming from some other portion of the urinary tract. It is generally observed that albumin is more frequently found and is of more significance when red blood cells are found microscopically.

TESTS FOR KNOWN QUANTITIES OF ALBUMIN

A second series of experiments was conducted in order to determine the comparative value of the tests when known quantities of albumin were placed in the urine. The material was prepared and tested as follows:

Large quantities of clear, normal urine negative for albumin by the heat and acetic acid test were used to dilute serum obtained from human blood. The total amount of protein was determined by multiplying the amount of protein nitrogen determined by the Kjeldahl method by the factor 6.25. In the serum used were 7.87 gm. of coagulable protein to each 100 c.c. A 1 per cent solution of protein based on this determination was made with the albumin-free urine. Each cubic centimeter of this urine contained 0.01 gm. of protein for each cubic centimeter. Further dilutions were made by taking specified amounts and making the volumes total 100 c.c., thus making concentrations from 400 parts of albumin to 100,000 to one part of 200,000. Fifty samples were prepared, four of them entirely free from albumin. These samples were given key letters and tested comparatively with heat and acetic acid, Stewart's, sulfosalicylic acid, and Heller's cold nitric acid test with an attempt to grade the quantity of albumin on the scale of 1, 2, 3, 4. The tests were made simultaneously without immediate comparison on the part of the persons carrying on the tests.

Table 4 has been arranged so as to show the different samples in order, according to the amount of albumin in each sample. It will be seen that Heller's test was positive in dilutions of 1 : 10,000 since one sample was reported to contain a questionable trace. A definite trace of albumin was reported by this test in a dilution of 1 : 8,000. Sulfosalicylic acid and Stewart's picric acid reagent showed a definite trace of albumin in the dilution of 1 : 100,000, while heat and acetic acid showed a trace of albumin in the dilution of 1 : 200,000. In the high concentrations the reports of the rough estimation of the quantity

TABLE 4
COMPARATIVE TESTS FOR ALBUMIN

Albumin, parts in 100,000.	Heat and acetic acid.	Stewart's reagent.	Sulfosalicylic acid.	Heller's test.	Albumin, parts in 100,000.	Heat and acetic acid.	Stewart's reagent.	Sulfosalicylic acid.	Heller's test.	Albumin, parts in 100,000.	Heat and acetic acid.	Stewart's reagent.	Sulfosalicylic acid.	Heller's test.
400	+++	+++	+++	+++	10.0	+++	+++	++	---	4.5	++	+++	+++	---
160	+++	+++	+++	+++	10.0	+++	+++	++	---	4.0	++	+++	+++	---
100	+++	+++	+++	+++	10.0	+++	+++	++	---	7.5	+++	+++	+++	---
80	+++	+++	+++	+++	9.5	+++	+++	+++	---	8.0	+++	+++	+++	---
80	+++	+++	+++	+++	9.0	+++	+++	+++	---	8.0	+++	+++	+++	---
70	+++	+++	+++	+++	8.5	+++	+++	+++	---	8.5	+++	+++	+++	---
60	+++	+++	+++	+++	8.0	+++	+++	+++	---	8.0	+++	+++	+++	---
50	+++	+++	+++	+++	8.0	+++	+++	+++	---	1.5	+++	+++	+++	---
40	+++	+++	+++	+++	7.5	+++	+++	+++	---	1.0	+++	+++	+++	---
30	+++	+++	+++	+++	7.5	+++	+++	+++	---	1.0	+++	+++	+++	---
25	+++	+++	+++	+++	7.0	+++	+++	+++	---	1.0	+++	+++	+++	---
20	+++	+++	+++	+++	6.5	+++	+++	+++	---	0.5	+++	+++	+++	---
20	+++	+++	+++	+++	6.0	+++	+++	+++	---	0.0	---	---	---	---
20	+++	+++	+++	+++	5.5	+++	+++	+++	---	0.0	---	---	---	---
15	+++	+++	+++	+++	5.0	+++	+++	+++	---	0.0	---	---	---	---
12.5	+++	+++	+++	+++	5.0	+++	+++	+++	---	0.0	---	---	---	---

TABLE 5
RELATIVE DEGREE OF SENSITIVITY

Method.	Positive, per cent.	Negative, per cent.	Sensitivity.
Heat and acetic acid.	92	8	1:900,000
Stewart.	88	12	1:100,000
Sulfosalicylic acid (80 per cent).	84	16	1:100,000
Heller (nitric acid).	84	66	1:8,000

Ninety-two per cent of samples contained albumin; 8 per cent of samples did not contain albumin.

were quite uniform. However, in the samples containing small quantities of coagulable protein, there was a discrepancy due to differences in individual judgment. In fact, in summing up our experiments with this series of tests, we were struck with the fallaciousness of attempting to judge accurately variations in the quantity of albumin, even on a scale of 1, 2, 3, 4. It seems that, at most, we are able only to state that we can detect a trace, a large amount, or a decidedly large amount of albumin.

The time element was an important factor in the ring tests of the three types used. The standard time of three minutes for cold nitric acid is probably necessary for sufficient coagulation to take place to be of much assistance in the evidence of the quantity of albumin present. Another valuable factor that might be noted is the method of mixing the reagent with the urine. If the contact is made in such a manner that there is little agitation of the urine on the surface of the reagent a dense ring may be formed, but the width of the band presented to the eye will be somewhat narrow. Slightly agitating the tube so as to bring the two fluids together over a larger surface contact will produce a more diffuse ring and sometimes will give a better basis for estimation for the amount of albumin. Another factor that seemed to be variable with all the tests was the differences that arose when one specimen of urine was compared with another, in order to determine whether one specimen contained more albumin than the other. The personal equation, which must always be considered in laboratory work, is, of course, another factor when an attempt is made to grade small amounts of albumin on varying scales. The relative degrees of sensitivity are further brought out in Table 4 with the four different methods. The summary in Table 5 shows that 92 per cent of specimens contained albumin and 8 per cent did not contain albumin. The heat and acetic acid test was positive in every instance up to the highest dilution used, 1 : 200,000; Stewart's test was positive in 82 per cent, sulfosalicylic acid in 84 per cent, both being sensitive to dilutions of 1 : 100,000. Nitric acid was positive in only 34 per cent; it was definitely sensitive in dilutions of 1 : 8,000. These ratios do not agree with those of Glaesgen, which are so often quoted. He used an Esbach albuminometer to determine the percentage of albumin in a specimen of urine containing albumin, dilutions being then made on this basis with albumin-free urine. This might account for the quantitative differences in his table and ours, although he reported

that heat and acetic acid were sensitive in dilutions of 1 : 130,000; the test performed by first acidulating, and then heating, was positive in dilutions of 1 : 180,000. The chief difference that he reported was that cold nitric acid was sensitive in dilution of 1 : 35,000. It is also generally stated that the sulfosalicylic acid test is more sensitive than is the heat and acetic acid test.

From this small series of comparative tests, and from the opinion that is formed from the thousands of urinalyses that are done annually in our laboratory, our conclusions are somewhat definite with regard to the relative merits of various methods and the actual possibility of estimating the quantity of albumin. Heat and acetic acid has been our standard test, and it is also the standard test in practically all laboratories. The chief objection to the method is that unnecessarily small amounts of albumin are detected, and other substances besides albumin give positive tests; thus the finding of a trace of albumin is always somewhat questionable.

We are strongly influenced to believe that the sulfosalicylic acid test should be considered standard. If this solution is used in 20 per cent strength, the ring test may be performed very rapidly and economically. Our technic is to place a few cubic centimeters of the reagent in a test tube, introduce the urine by means of a piece of one-quarter-inch glass tubing of convenient length, the contact ring being formed in the tubing. Stewart's picric acid test is also an inexpensive and rapid test, and seems to be all that is claimed for it by the author. The only objection to it that we might raise is that uric acid and creatinin, substances that interfere with the accuracy of the Esbach quantitative test, might also interfere theoretically with a qualitative test for albumin.

It seems to us that the quantitative determinations of slight amounts of albumin are open to great variation, namely, variations in technic and differences in the judgment of technicians. If this is of vital significance, it would seem advisable to devise some simple, accurate, quick method for more easily estimating the quantity of coagulable protein in urine. Folin and Denis have outlined a procedure, using sulfosalicylic acid, that is applicable to the estimation of albumin that is not time consuming. It necessitates, however, the preparation of standards made from human blood serum, in which the amount of serum albumin has been estimated. This requires more accurate methods than are usually at the disposal of a urinalysis laboratory.

The method depends on reading the degree of turbidity produced by the precipitation of albumin with sulfosalicylic acid, against the albumin standard in a Duboscq colorimeter. We have thought that possibly the method could be modified, so that a rough estimate could be made, by using a permanent standard made from some insoluble substance like barium sulfate.

CLINICAL STUDIES; SLIGHT ALBUMINURIA

The real question before us today is the importance that is to be attached to the finding of traces of albumin in the urine by any accepted method. To record the clinician's point of view on this subject, instead of merely to tabulate statistics from histories in our files, we decided to make an intensive study of current cases at the Mayo Clinic. One of us (Conner) assumed the task of eliciting the clinical evidence from cases that were selected in this group. During the period of study (two months) 663 patients registered in the section. The usual procedure is the examination of a twenty-four-hour specimen of urine. More than one-third of the patients, 262 in the group of 663, showed on preliminary examination some albumin in the urine by heat and acetic acid. For many reasons it was impossible to study the entire group intensively, but seventy unselected patients, forty males and thirty females, were completely studied from the viewpoint of the life insurance examiner. The basis for the clinical diagnosis is presented in the Tables 6, 7, and 8. The following points were considered: history of previous disease, scarlet fever, measles, diphtheria, malaria, typhoid fever, pneumonia, tonsillitis, sinus infection, tooth infection, lead poisoning, alcoholism, and albuminuria in pregnancy. Emphasis was laid on symptoms of nocturia, pollakiuria, polyuria, oliguria, hematuria, dysuria, urinary suppression, urinary retention, pain in the kidney region, history of high blood pressure, history of stroke, dyspnea, orthopnea, history of ascites, history of enlarged liver, history of edema, headache, dizziness, disturbance of vision, uremic convulsions, uremic delirium, uremic coma, uremic drowsiness, uremic nausea, uremic vomiting, uremic diarrhea, epistaxis, pasty face, and special kidney symptoms.

The following points in the physical examination were emphasized: systolic blood pressure, diastolic blood pressure, pulse, temperature, weight, normal weight, heart murmurs, cardiac enlargement, accentuated aortic second sound, arteriosclerosis (radial, brachial, temporal,

TABLE 6
CLINICAL DISEASE OF THE KIDNEY

Case.	Age.	Sex.	Systolic blood pressure.	Diastolic blood pressure.	Urinalysis.				Blood urea mg. per 100 c.c.	Blood uric acid mg. per 100 c.c.	Phenolsulphone-phthalein test.	Clinical diagnosis (other than renal).	Renal diagnosis.	Basis of renal diagnosis.
					Urine amount.	Specific gravity.	Albumin.	Microscopic.						
A114878	62	F.	230	116	?	1018	1	Ca ²⁺ . Pus. Ca ²⁺ . Pus.	52	2.8	35	Hypertension, arteriosclerosis.	Moderate chronic nephritis.	Nocturia; stroke of paralysis (slight); dyspnea; vertigo; blood pressure; arteriosclerosis; arcus senilis; albuminuria; hyaline casts; pus; blood urea; phenolsulphone-phthalein.
A38061	54	M.	160	110	600	1026	5	Ca ²⁺ . Pus. Blood. Ca ²⁺ . Pus. Blood.	38	2.0	50	Arteriosclerosis; bronchial asthma; dental infection; small left varicocele.	Chronic nephritis.	Nocturia; dyspnea; headache; systolic blood pressure 160; diastolic 110; fundus; albuminuria; microscopic.
A340860	29	M.	140	84	750 1200	1024 1023	5 2	Ca ²⁺ . Pus. Ca ²⁺ . Pus.	26		55	Pulmonary (?) and glandular tuberculosis.	Mild nephritis.	Frequency; headache; vomiting; epistaxis; blood pressure; systolic 140; diastolic 84; arteriosclerosis; albuminuria; casts.
A388719	45	M.	144	88	1600 2100 1700	1015 1012 1013	1 1 1	Ca ²⁺ . Blood. Blood. Blood.	52	3.2 2.8	40 55	Chronic arthritis; chronic tonsillitis; dental infection; secondary anemia.	Mild chronic nephritis.	Nocturia; headache; blood pressure; microscopic; phenolsulphonephthalein; blood uric acid; blood urea.
A341021	39	M.	182	92	950 750	1029 1027	1 1	Negative. Pus. Negative.	54	2.1	55 45	Mild hypertension and arteriosclerosis; mild ichthyosis; chronic tonsillitis.	Mild chronic nephritis.	Blood pressure; cardiac hypertrophy; arteriosclerosis; albuminuria; blood urea.
A341846	46	M.	210	120	600 1550	1016 1013	1 2	Negative. Ca ²⁺ . Blood.	48	2.5	40	Bilateral inguinal hernia.	Chronic nephritis.	Nocturia; dyspnea; vertigo; cardiac hypertrophy; blood pressure; fundus; albuminuria; casts; blood urea; phenolsulphonephthalein.

CLINICAL DISEASE OF THE KIDNEY—Continued

A345001	65	M.	180	80	550	1027	1	Casts.	58		50	Angina pectoris; arteriosclerosis.	Mild chronic nephritis.	Dyspnea; headache; vertigo; accent A 2; fundus; albuminuria; casts; blood urea.
A341339	58	M.	140	70	700 1100	1025 1023	1 1	Pus. Blood. Pus. Blood.	52 46	2.8 2.8	20 40	Prostatic hypertrophy; mild arteriosclerosis.	Mild chronic nephritis.	Arteriosclerosis; phenolsulphonethalein; blood uric acid; blood urea; albuminuria; microscopic.
A340275	56	M.	180	110	800	1021	1	Pus.	38	4.0	50	Double direct inguinal hernia; myocarditis.	Mild pyelonephritis.	Nocturia; pain kidney region; blood pressure; accent A 2; arteriosclerosis; albuminuria; microscopic; blood uric acid.
A337782	52	M.	125	80	850 600	? 1027	2 2	Blood. Pus. Casts.	32	2.0	50	Chronic tonsillitis; dental infection.	Mild nephritis.	Albuminuria; microscopic.
A341089	60	M.	160	100	1200 1400	1021 1021	1 1	Casts. Casts.	24	3.1	25 50	Mitral insufficiency; myocardial degeneration; chronic cholecystitis; dental infection.	Mild nephritis.	Nocturia; polyuria; dyspnea; blood pressure; cardiac hypertrophy; arteriosclerosis; edema; albuminuria; phenolsulphonethalein; blood uric acid.
A339900	49	F.	158 168	68	1150 850	1010 1006	1 1	Pus.	18	2.2	40 45	Hypertension; arteriosclerosis; chronic cholecystitis; constipation; chronic tonsillitis; dental sepsis.	Mild nephritis.	Nocturia; hypertension; albuminuria; low specific gravity; phenolsulphonethalein.
A343588	61	M.	180	105	350 480	1025 1024	1 1	Casts. Casts.	40 36	3.07	40	Abdominal tumor right upper quadrant.	Moderate chronic nephritis.	Nocturia; vertigo; cardiac hypertrophy; accentuated A 2; arteriosclerosis; fundus; albuminuria; microscopic; phenolsulphonethalein; blood uric acid.
A342499	43	F.	228	108	2000 2000	1019 1019	1	Negative. Negative.	40 30	1.6	40 50	Moderate arteriosclerosis; myocardial insufficiency; septic tonsils; diabetes mellitus.	Chronic nephritis.	Nocturia; polyuria; day frequency; hypertension; dyspnea; headache; vertigo; cardiac hypertrophy; accentuated A 2; fundus; arteriosclerosis; albuminuria; blood urea; phenolsulphonethalein.

CLINICAL DISEASE OF THE KIDNEY—Continued

Case.	Age.	Sex.	Systolic blood pressure.	Diastolic blood pressure.	Urinalysis.				Blood urea mg. per 100 c.c.	Blood uric acid mg. per 100 c.c.	Phenolsulphone-phthalein test.	Clinical diagnosis (other than renal).	Renal diagnosis.	Basis of renal diagnosis.
					Urine amount.	Specific gravity.	Albumin.	Microscopic.						
A875102	44	F.	170	110	775 1200	1012 1012	1 2	Blood. Pus. Pus. Blood.	40 28	2.6 2.6	45 50	None.	Bilateral pyelonephritis on mild chronic nephritis.	Nocturia; day frequency; dysuria; blood pressure; accentuated A 2; fundus; albuminuria; microscopic; blood urea; phenolsulphone-phthalein.
A838218	47	M.	160	98	1200 2000 500	1010 1014 1019	3 3 2	Negative. Negative. Negative.	18 30	5.0	35	Polycythemia.	Chronic nephritis.	Hypertension; headache; vertigo; uremic convulsion; cardiac hypertrophy; accentuated A 2; disturbance of vision; fundus; albuminuria; phenolsulphonephthalein; blood uric acid.
A840000	57	M.	180 190	96 100	450 600 600	1027 1028 1028	4 3 4	Casts. Casts. Casts.	28	2.7	30 20 65	Cardiovascular renal disease with vascular and heart symptoms predominant.	Chronic nephritis.	Albuminuria; nocturia; hypertension; slight stroke; dyspnea; edema; tinnitus; cardiac hypertrophy; accentuated A 2; arteriosclerosis; fundus; microscopic; phenolsulphonephthalein.
A842235	19	F.	112	82	1440 1600	1012 1011	2 2	Pus. Pus.	24	2.0	35 45	None.	Bilateral pyelonephritis.	Nocturia; day frequency; hematuria; dysuria; pain in region of kidney; albuminuria; microscopic; low specific gravity; phenolsulphonephthalein.
A842063	66	M.	150	100	725 700	1020 1020	1 1	Casts. Casts. Blood.	26 26	3.7	15 15	Emphysema; chronic bronchitis and nontuberculous lung infection.	Chronic nephritis.	Nocturia; polyuria; day frequency; dyspnea; blood pressure; cardiac hypertrophy; arteriosclerosis; albuminuria; microscopic; blood uric acid; blood urea; phenolsulphonephthalein.

A330073	42	F.	230	140	400 1000 550 850	1098 1018 1080 1018	1 2 1 2	Pus. Pus. Blood. Negative.	32 38	30 65	Hypertension; marked neu- rosis; chronic cholecystitis; chronic tonsillitis; dental infection.	Chronic nephritis.	Nocturia; day frequency; dyspnea; headache; ver- tigo; blood pressure; ac- centuated A ₂ ; cardiac hy- pertrophy; albuminuria.
A330096	47	F.	200	140	1350 1000	1014 1080	1 2	Cast.	40	35	Hypertension; prolapsed uterus with cystocele.	Chronic nephritis.	Nocturia; hypertension; dyspnea; headache; ver- tigo; disturbance of vision; fluidus; blood pressure; ac- centuated A ₂ ; arterioscle- rosis; albuminuria; mi- croscopic; pyelitis; blood urea.
A342111	49	F.	210 190	180 96	500 675	1084 1013	1 1	Pus. Casts. Pus.	30	50	Hypertension; mucous coli- tus; chronic constipation.	Chronic nephritis.	Nocturia; history of scarlet fever; hypertension; head- ache; vertigo; blood pres- sure; cardiac hypertrophy; accentuated A ₂ ; arterio- sclerosis; albuminuria; mi- croscopic; blood ure acid.
A340260	43	F.	205	120	1700 1400	1007 1008	4 4	Blood. Pus. Pus.	180	10	Hypertension; arterioscle- rosis.	Marked chronic nephritis.	Nocturia; hematuria; pain in kidney region; hyperten- sion; dyspnea; edema; ver- tigo; disturbance of vision; fluidus; uremia; blood pressure; cardiac hyper- trophy; accentuated A ₂ ; arteriosclerosis; low specific gravity; albuminuria; mi- croscopic; blood ure acid; blood urea; phenolsulphone- phthalein.
A340546	34	F.	106	66	500 430	1018 1013	1 1	Pus.	34	30	Pelvic malignancy origin un- determined.	Infected hydronephrosis, right.	Cystoscopic; albuminuria; phenolsulphonephthalein; microscopic.
A341707	33	F.	110	80	1150 1100	1009 1007	1 1	Pus. Pus. Blood.	20	50	None.	Right hydronephrosis with stones.	Nocturia; hematuria; pain in kidney region; microscopic; urogenital; cystoscopic pyelogram.
A342856	52	M.	125	65	700 370	1092 1092	1 1	Pus. Casts. Pus.	50 54	50	None.	Stone right ureter, probably some nephritis.	Day frequency; hematuria; kidney colic; roentgen ray; cystoscopic; albuminuria; microscopic; blood urea.

CLINICAL DISEASE OF THE KIDNEY—Concluded

Case.	Age.	Sex.	Systolic blood pressure.	Diastolic blood pressure.	Urinalysis.				Blood urea mg. per 100 c.c.	Blood uric acid mg. per 100 c.c.	Phenolphthalein test.	Clinical diagnosis (other than renal).	Renal diagnosis.	Basis of renal diagnosis.
					Urine amount.	Specific gravity.	Albumin.	Microscopic.						
A342561	40	M.	130	100	9000 1950	1013 1015	2 2	Pus. Pus. Blood.	42 34	3.8	15	Dyspitarism; encephalitis; ketargies (residue); bladder diverticulum.	Left pyelonephritis on chronic nephritis.	Nocturia; polyuria; day frequency; urinary retention; dysuria; edema; headache; drowsiness; epistaxis; albuminuria; microscopic; blood urea; phenolphthalein; phthalein; blood uric acid.
A342526	29	M.	114	80	1000 800	1015 1015	3 3	Pus. Blood. Pus. Blood. Tb. +	38 32	3.7	45	None.	Right renal tuberculosis.	Nocturia; frequency; hematuria; albuminuria; microscopic; cystoscopic; pyelogram; phenolphthalein; phthalein.
A34347	45	F.	152 168	88 94	650 350	1027 1028	1 1	Pus. Blood. Pus. Blood.	36	3.2	50	Nervousness, small cervical polyp; constipation; mild pruritis ani; dental sepsis; secondary anemia.	Very mild nephritis.	Nocturia; headache; edema?; accentuated A & albuminuria; microscopic; blood uric acid.

arcus senilis), tenderness (kidney region, bladder region), pasty face, edema (feet, eyelids, general anasarca, ascites, hydrothorax), examination of the fundus, examination of the tonsils, examination of the teeth (including roentgen examination), roentgen examination of the kidney, the ureter and bladder, and cystoscopic examination when indicated.

Examination of the fundus in the special section devoted to the eye was made a part of the routine examination in a large proportion of the cases. A phenolsulphonephthalein test of the renal function, intravenous wherever possible, was made in all cases. In all cases two twenty-four-hour specimens of urine were examined, and blood urea, blood uric acid, and blood Wassermann tests were made. The special history was taken as soon as albumin was found in the urine; the history was not colored by the laboratory findings. After all the material had been collected, the general history, the special history sheet, and all laboratory findings were consulted and the diagnosis made of the presence or absence of renal disease. No effort was made in these studies to divide the cases into the various types of renal diseases. Because of the purpose of this study, that is, to determine insurability, the patients were divided into three groups: patients without kidney lesions, patients with doubtful kidney lesions, and patients with clinically definite kidney lesions. In considering the importance of the laboratory tests in the diagnosis of renal diseases, a reading of from 40 to 50 per cent was made the dividing line. We considered it possible to have as low a phenolsulphonephthalein return as 40 per cent in normal patients or, conversely, as high as 50 per cent in patients that would otherwise be considered nephritic. Likewise, from 35 to 50 mg., of urea for each 100 c.c. of blood was taken as the dividing line between the normal and the abnormal; that is, we considered it possible to find as low as 35 mg. of urea for each 100 c.c. of blood in patients otherwise definitely nephritic, or as high as 50 mg. in patients otherwise normal. It is our rule to have blood taken for urea determination when the patient is fasting. On account of the practically constant uric acid content of the blood in normal persons on various diets and under various conditions we have considered, if other indications were present, anything above 2.5 mg. for each 100 c.c. as probable evidence of some impairment of kidney function. We have considered specific gravity above 1.010 as normal if there were no other indications of nephritis. Hyaline casts were not considered

TABLE 7
QUESTIONABLE DISEASES OF THE KIDNEY

Case.	Age.	Sex.	Systolic blood pressure.	Diastolic blood pressure.	Urinalysis.				Blood urea mg. per 100 c.c.	Blood uric acid mg. per 100 c.c.	Phenolsulphone test.	Clinical diagnosis (other than renal).	Renal diagnosis.	Basis of renal diagnosis.
					Urine amount.	Specific gravity.	Albumin.	Microscopic.						
A318867	27	F.	140	80	675 1000	1011 1009	1 1	Casts. Pus. Pus.	30	1.7	45	Myocarditis with cardiac neurosis; colloid goiter; partial atresia of vagina.	Possible mild nephritis.	Albuminuria; low specific gravity; one hyaline cast in field; phenolsulphone-phthalein.
A342928	58	M.	134	68	625 650	1028 1031	1 1	Casts. Blood. Negative.	38	2.3		Carcinoma of gallbladder.	Probable very mild nephritis.	Occasional nocturia; slight headache; arteriosclerosis; albuminuria; microscopic.
A342739	33	F.	112	68	1100 900	1018 1015	1 1	Pus Pus.	20 28	1.7	40	Mild pericarditis; chronic tonsillitis; tuberculosis suspected.	Possible mild pyelonephritis.	Nocturia; day frequency; albuminuria; phenolsulphone-phthalein; microscopic; history of pyuria.
A327813	24	M.	144	84	600* 1150	1030 1024	1 0	Blood. Blood.	26	2.5	40	Tuberculosis suspected.	Possible renal disease.	Slight hypertension; albuminuria; microscopic; phenolsulphonephthalein.
A343579	31	M.	102	65	750 ?	1029 1024	0 1	Casts. Pus.	44	3.4	65	Very marked neurosis; chronic tonsillitis.	Probable slight nephritis.	Frequency; albuminuria; casts; blood urea; blood uric acid.
A343090	36	M.	120	62	1850 1925	1013 1008	1 0	Negative. Negative.	26 32	3.6	50	Achylia gastrica; pyorrhea.	Possible very mild chronic nephritis.	Slight nocturia; slight headache; vertigo; slight arteriosclerosis; albuminuria; blood uric acid.
A341588	28	M.	130	85	1000 1500	1025 1016	2 1	Blood. Negative.	40 36	1.4	55	Psychoneurosis; muscular rheumatic pains of chest; chronic constipation.	Probable very mild nephritis.	Hematuria during measles; albuminuria; microscopic; accentuated A. g.
A340069	61	F.	140	100	650 ?	1006 1006	1 1	Blood. Pus. Blood. Pus.	40	3.0	50	Old pleurisy left base; mild chronic bronchitis; mild myocardial insufficiency.	Possible chronic nephritis.	Blood pressure; albuminuria; blood urea; low specific gravity; phenolsulphone-phthalein (normal).

* Twelve-hour specimen.

QUESTIONABLE DISEASES OF THE KIDNEY—Continued.

A340183	36	F.	113	76	1000 1050	1011	1010	1016 1014	92	60	Bilateral pulmonary tuberculosis and arthritis.	Probable very mild nephritis.	Low specific gravity; albuminuria.
						1	2						
A342003	37	F.	110	60	625 700	9		1016 1014	Negative, Negative, 18	60	Postoperative adhesions; constipation; achylia gastrica; secondary anemia.	Probable mild nephritis.	"Kidney trouble" during pregnancy; frequency; nocturia; headache; vertigo; edema; albuminuria; secondary anemia.
A343173	46	M.	98	60	1550 2050	1013 1012	1		Pus. Pus.	50 50	Exophthalmic goiter.	Probable mild chronic nephritis.	Nocturia; headache; arteriosclerosis; fundus (fullness of veins); albuminuria; blood uric acid.
A342897	61	M.	110	70	625 550	1029 1026	1		Negative, Negative, 32	50	Bronchial asthma.	Probable very mild nephritis.	Nocturia; headache; slight arteriosclerosis; slight albuminuria; uric acid.
A337732	59	M.	125	72	700 1800	1024 1022	1		Negative, Negative, 38	20 45	Hypertrophy of prostate.	Probable mild nephritis.	Nocturia; edema; vertigo; albuminuria; phenolsulphonephthalein.
A340597	57	M.	122	74	750 700	1025 1005	1		Blood, Casts.	50	Right inguinal hernia.	No kidney disease(?).	Occasional headache; arteriosclerosis; albuminuria; occasional casts.
A339553	31	F.	118	80	1200 1250	1021 1017	1		Blood, Blood.	45	None.	Mild nephritis(?).	Hematuria; albuminuria; microscopic; phenolsulphonephthalein.
A341014	57	M.	140	90	700 900	1020 1020	1		Blood, Pus. Blood, Pus.	55 45	Hypertrophy of prostate.	Probable slight nephritis.	Nocturia; headache; vertigo; arteriosclerosis; albuminuria; blood uric acid.
A324717	47	F.	110	82	1550	1009	1		Pus.	65 45	Lacerated cervix and perineum; cystic cervicitis; hypertrophic endometritis; mitral regurgitation; chronic tonsillitis; dental infection; marked nervousness.	No kidney disease(?).	Albuminuria; low specific gravity; nocturia.
A343491	42	M.	120	80	950 ?	1029 1030	0		Pus. Pus.	33 40	Unilateral hernia; obesity; chronic tonsillitis; dental infection.	Probable mild chronic nephritis.	Albuminuria; phenolsulphonephthalein; blood uric acid.
A338792	54	M.	178	100	600 800	1021 1021	1		Negative, Negative, 28	35 55	Angina pectoris; chronic myocarditis; arteriosclerosis with hypertension.	Probable chronic nephritis.	Hypertension; edema; albuminuria; phenolsulphonephthalein; hypertension; retinal arteriosclerosis; general arteriosclerosis.
A342634	21	M.	120	60	1050 1600	1013 1012	2		Casts, Negative.	50	Acute on chronic endocarditis.	Probable mild nephritis.	Albuminuria; microscopic.

TABLE 8
KIDNEY DISEASE ABSENT (CLINICALLY)

Case.	Age.	Sex.	Systolic blood pressure.	Diastolic blood pressure.	Urinalysis.				Blood urea mg. per 100 c.c.	Blood ureic acid mg. per 100 c.c.	Phenolsulphonhalein test.	Clinical diagnosis (other than renal)	Renal diagnosis.
					Urine amount.	Specific gravity.	Albumin.	Microscopic.					
A39831	24	M.	110	68	?	1032	1	Negative.	28 24	4.5	55	Chronic tonsillitis; chronic bronchitis.	No kidney disease.
A342060	23	F.	120	80	425	1030	1	Pus. Blood. Pus. Blood.	24	1.8	50	Leukorrhea.	No kidney disease.
A340289	25	M.	124	70	1700	1030	1	Pus.	24	2.5	65	Neurosis; mild dental sepsis.	No kidney disease.
A341076	16	F.	118	72	700 400	1025 1016	1 1	Negative. Pus.	20	2.4	60	Bronchiectasis; probably chronic sinusitis; chronic tonsillitis.	No kidney disease.
A342901	38	F.	106	66	625 750	1025 1017	1 1	Negative. Negative.	24 26	2.1	55	Bronchial asthma; nasal polyp; retroverted uterus; lacerated cervix; prolapse of ovaries.	No kidney disease.
A342157	23	M.	120	70	400 800	1026 1024	1 1	Negative. Negative.	26	3.3	55	Pulmonary tuberculosis (bilateral, advanced with cavity formation).	No kidney disease.
A342304	34	F.	108	68	400 350	1024 1034	1 0	Pus. Pus.	28	2.3	45	Lacerated perineum; lacerated cervix; metrorrhagia; neurosis.	No kidney disease.
A340982	21	M.	108	68	400 350	1020 1029	1 1	Negative. Negative.	30	2.0	80	Diarrhea of indeterminate etiology; (pancreatic? nervous?); migraine 75 per cent; diabetes?	No kidney disease.
A341637	40	F.	130	80	800 900	1015 1011	1 0	Negative. Negative.	26	1.3	60	Adenoma of thyroid; nontoxic; cholecystitis 25 per cent; general debility.	No kidney disease.
A343023	29	F.	120	64	875 800	1016 1017	1 1	Negative. Negative.	32	1.3	55	Neurosis (hysteria); migraine; leukorrhea; lacerated cervix and cystic cervicitis.	No kidney disease.
A340263	43	F.	136	72	1525	1010	1	Pus.	20	2.1	60 65	Chronic nervous exhaustion; fibroma of uterus; coccygodynia; dental sepsis	No kidney disease.
A340206	39	F.	134	90	750 400	1010 1016	1 1	Pus. Blood. Pus.	18	3.0	50	Bronchiectasis.	No kidney disease; blood & due to men- struation.

KIDNEY DISEASE ABSENT (CLINICALLY)—Continued

A340472	60	M.	180	78	360	1080	1	Negative.	46		60	Carcinoma of lower end of esophagus.	No kidney disease.
A343333	21	M.	104	66	875	1013	1	Negative.	28		55	Septic tonsils; chronic appendicitis 60 to 75 per cent.	No kidney disease.
A340455	27	M.	132	84	950 350	1084 1028	1 1		36	2.5	65	Epilepsy; central nervous system syphilis?	No kidney disease.
A325661	26	F.	112	70	500 445	1024 1018	1 1	Cast, pus.	22	3.1	60	Jaundice following treatment for syphilis; latent syphilis.	No kidney disease.
A337638	28	F.	123	76	275 550 950	1080 1080 1011	1 0 0	Pus. Pus. Pus.	20 18	1.4 1.7	50 50	Nontuberculous lung infection; possibly mild chronic appendicitis; psychoneurotic headaches; constipation.	No kidney disease; "Kidney trouble" during pregnancy.
A316354	40	M.	125	80	975 900	1023 1025	1 1	Pus. Pus.	46 54	2.4	55	Central nervous system syphilis; cystitis.	No kidney disease.
A338131	25	M.	126	76	400 1800	1032 1021	1 0	Negative. Negative.	34	2.3	55	Syphilis.	No kidney disease.
A314539	27	F.	112	72	300	1023	1	Pus.	22	2.8		Leukorrhea following operation making artificial vagina.	No kidney disease.
A343681	29	F.	118	80	400 550	1027 1031	1 1	Negative. Pus.	32	2.1	55	Pyorrhea alveolaris; fatigue (overwork)	No kidney disease; "Kidney trouble" during pregnancy.

definite evidence of kidney disease, except when other evidence was present. Granular casts were considered definite indication of a kidney lesion. If a woman, for obvious reasons, has a considerable amount of blood or pus in the urine, the value of albuminuria is somewhat discounted. If a woman had blood or pus in the urine, a single specimen was taken after a douche, whenever possible. In instances in which it was warranted catheterization was done in order to be as certain as possible of the origin of the pus or blood. Cystoscopic examination was made only when indicated by the symptoms, laboratory signs, or roentgen-ray findings. In cases of definite arteriosclerosis with hypertension, even with good kidney function as shown by the tests for phenolsulphonephthalein, blood urea, and uric acid, we assumed that there was probably some damage to the kidney as part of the process. One symptom, sign, or laboratory finding, even if very definite, was not accepted as sufficient for the diagnosis; we considered all symptoms, signs, and laboratory findings together, making the attempt to give each its proper value.

In summarizing the protocols of the clinical study of these seventy cases, it is seen that a definite lesion in the kidney was found in 40 per cent; a doubtful lesion and no lesion were each represented by 30 per cent. While it is evident that in a large proportion of the cases albuminuria is associated with kidney disease, we must admit that albuminuria in itself is of no clinical significance. In all of these groups are persons who would be rejected for life insurance on grounds other than that of the consideration of renal pathology. But, considering the group as a whole, who could have said which one of the persons, merely from the point of albuminuria, would present findings which would be the cause of rejection for life insurance because of real impairment to kidney function? Are all of those persons who were considered not to have lesions of the kidney, which constitute nearly one-third of the total, to be excluded from life insurance because of the finding of albumin in the urine?

FUNCTIONAL TESTS

In connection with this clinical study and as a basis for diagnosis it is seen in Tables 6, 7 and 8 that in many instances special laboratory tests were used to add evidence on which a basis could be formed for clinical diagnosis.

For many years there have been attempts to develop some method

for determining the efficiency of kidney function, and during this time many methods have been proposed. In the main, those methods do not reveal a pathologic condition of the kidney until it is so marked that the ordinary laboratory and clinical tests are sufficient to diagnose the case. Thus, the methods resolve themselves into tests for the degree of function in a case of a recognized kidney lesion. It has been shown to a fair degree of absolutism that the first nitrogenous substance that a kidney fails to excrete properly is uric acid, the next urea, and the third creatinin. Thus, an elevated blood uric acid occurs before an elevation of urea, and the latter before there is a rise in creatinin. However, many patients seem to have some damage to the kidney when the blood uric acid is marginal, that is, between 2.5 and 3.5 mg. for each 100 c.c. Again, in this particular investigation, it was necessary to determine whether or not there was damage to the kidney in certain cases in which albumin was shown in the urine.

As a test for very early lesions in the kidney, or minor derangements of kidney function, it has been suggested that if the body were given an excess of uric acid to eliminate, it might show a difference in ability to eliminate it according to whether or not the kidneys were damaged.

Denis showed that persons with nephritis exhibit an accumulative effect of uric acid in the blood if fed on high purin diets, while normal persons have no change in the blood uric acid under these conditions. Upham and Highley pointed out the necessity of keeping patients on a constant purin intake, in order to compare and study determinations of blood uric acid.

MAGATH URIC ACID CONCENTRATION TEST

In order to test the ability of the kidneys to excrete uric acid a concentration test was carried out in the following manner: The patient was given 0.8 gm. of caffein citrate in two or three doses during three hours, after a sample of blood for uric acid determination had been taken. The urine was saved for the next twenty-four hours, and at the end of that time another sample of blood was taken for uric acid determination. The two results were compared and uric acid was determined in the twenty-four-hour sample of urine and compared with the amount in the twenty-four-hour sample collected just before the administration of caffein. Typically in a normal person the effect is quite definite, a diuretic effect which results in a lowering of the

blood uric acid by not more than 0.3 mg. for each 100 c.c., and an elevation of uric acid in the urine of about 0.6 gm. In a typical nephritic patient there is an elevation of about 0.6 mg. for each 100 c.c. in the blood and practically no change in the urine, either in uric acid content or volume. The use of caffeine for such a test demands some explanation and justification.

Caffein belongs to the group of substances known as purins, of which uric acid is a well known member. Caffein is 1, 3, 7, trimethylxanthin.

The manner of excreting caffeine is a subject concerning which there is a difference of opinion. Sollmann says that it is completely and readily absorbed, and that very little is excreted as such. Salant and Rieger found that in carnivora there is only 1 per cent excreted as such, while in herbivora about 6 to 8 per cent is excreted as caffeine. Sollmann further states that from 10 to 40 per cent of the substance loses its methyl groups and is excreted as dimethylxanthin or monomethylxanthin, while up to 80 per cent is excreted as urea, practically none as uric acid. Cushny states that the uric acid of the urine is not increased by the ingestion of caffeine. On the other hand, Greene states that caffeine is demethylated in the body and forms xanthin, which is excreted in the manner in which any animal xanthin is excreted, namely, as uric acid. Schittenhelm found that feeding caffeine increases the amount of uric acid in the urine, and Strauss obtained an addition in the amount of uric acid in the urine of 45 per cent after the ingestion of 2 gm. The justification of the dose of 0.8 gm. is made on the grounds that the fatal dose is probably more than 20 gm., that a safe dose is certainly up to 2 gm., that the United States Pharmacopeia dose is 0.3 gm., and the British Pharmacopeia dose 0.6 gm.

If caffeine is burned to uric acid in the body the reaction probably is along this line: Caffein—dimethylxanthin—monomethylxanthin—xanthin—uric acid. If under the conditions of the tests caffeine were not burned to uric acid, the results would be explained on other grounds. Two explanations present themselves at present: first, that caffeine is burned in the body to some close relative of uric acid, excreted, giving reactions similar to those of uric acid by the method used (Folin and Wu); second, that caffeine stimulates the excretion of uric acid in normal kidneys, and in pathologic kidneys causes the rise of uric acid in the blood by stimulating the production of it in the body. This may be an effect of positive or negative diuresis.

A group of the cases studied by Conner was selected for study of

TABLE 9
NO LESIONS OF THE KIDNEY

Case.	Diagnosis of nephritis (Conner).	Blood uric acid 1.	Blood uric acid g.	Difference between 1 and g.	Urine uric acid 1.	Urine uric acid g.	Difference between 1 and g.	Remarks.
A326601	Syphilis.	3.4	3.4	+0.0	0.47	0.49	+0.02	Treatment for syphilis.
A345093	Necrosis, migraine, syphilis.	1.3	3.1	+1.8	0.41	0.40	-0.01	0.4 gm. caffein.*
A348157	Pulmonary tuberculosis.	3.2	3.4	+0.2	0.35	0.35	+0.01	
A348901	Benign asthma, prolapse of ovaries.	2.1	1.9	-0.2	0.31	0.37	+0.06	
A341589	Artificial vagina.	2.0	2.8	+0.8	0.35	0.37	+0.02	Treatment for syphilis.
A340455	Epilepsy, central nervous system syphilis.	1.5	2.9	+0.4	0.39	0.38	-0.01	
A348900	Leukorrhea.	1.3	3.0	+0.3	0.38	0.38	+0.00	
A348904	Metrorrhagia, neurosis.	2.3	1.7	-0.4	0.19	0.31	+0.12	
A341074	Chronic sinusitis.	2.4	1.7	-0.7	0.68	0.89	+0.21	Treatment for syphilis.
A310633	Central nervous system syphilis, cystitis.	2.5	3.3	+1.0	0.76	0.68	-0.08	
A340683	Diarrhea, pancreatitis.	2.0	3.3	+0.9	0.40	0.43	+0.03	

* Full dose is 0.8 gm. caffein.

TABLE 10

LESIONS OF THE KIDNEY

Case.	Renal diagnosis.	Clinical diagnosis (other than renal).	Blood uric acid 1.	Blood uric acid g.	Difference between 1 and g.	Urine uric acid 1.	Urine uric acid g.	Difference between 1 and g.	Remarks.
A341014	Hypertrophy of prostate.	Probably slight nephritis.	3.1	2.3	-0.8	0.60	0.77	+0.17	
A343173	Exophthalmic goiter.	Probably mild chronic nephritis with arteriosclerosis.	3.8	3.2	-0.6	0.73	0.51	-0.22	Twelve-hour specimen urine.
A348739	Pericarditis.	Possibly mild pyelonephritis.	1.7	1.9	+0.2	0.30	0.25	-0.05	0.4 gm. caffein.*
A348987	Bronchial asthma.	Probably mild nephritis.	3.0	2.8	-0.2	0.58	0.58	+0.00	Eighteen-hour specimen urine.
A340069	Myocarditis.	Possibly nephritis.	3.0	3.0	+0.0	0.56	0.54	-0.02	
A341588	Chronic constipation; psychoneurosis.	Possibly mild nephritis.	1.4	2.5	+1.1	0.63	0.74	+0.11	
A324717	Dental infection, nervousness.	No lesion of the kidney (?).	1.4	1.7	+0.3	0.38	0.50	+0.12	
A343603	Anemia, gastritis.	Probably mild nephritis.	1.4	1.8	+0.4	0.33	0.32	-0.01	
A340397	Hernia.	No lesion of the kidney (?).	2.4	1.9	-0.7	0.19	0.46	+0.27	
A338792	Hypertension.	Probably some chronic nephritis.	2.6	3.3	+0.7	0.55	0.46	-0.09	
A433090	Achylia gastrica, pyorrhea.	Possibly mild chronic nephritis.	3.6	3.8	+0.2	0.67	0.42	-0.25	

* Full dose is 0.8 gm. caffein.

TABLE 11
DEFINITE LESION OF THE KIDNEY (CLINICALLY)

Case.	General diagnosis (Conner).	Blood uric acid 1.	Blood uric acid 2.	Difference between 1 and 2.	Urine uric acid 1.	Urine uric acid 2.	Difference between 1 and 2.	Remarks.
A338961	Chronic nephritis, arteriosclerosis	2.0	2.8	+0.8	0.42	0.29	-0.13	0.4 gm. caffein,* eighteen-hour specimen of urine.
A342561	Left pyelonephritis with chronic nephritis	3.8	3.3	-0.5	0.70	0.99	+0.29	
A341707	Hydronephrosis with stones, nephritis	1.9	2.5	+0.6	0.26	0.39	+0.13	
A340246	Infected hydronephrosis	2.4	3.1	+0.7	0.13	0.42	+0.19	
A341689	Mild nephritis, arteriosclerosis, hypertension	2.2	3.5	+1.3	0.83	1.00	+0.17	
A339900	Mild nephritis	2.2	3.0	+0.8	0.26	0.28	+0.02	
A341621	Mild chronic nephritis, hypertension, arteriosclerosis	2.1	2.8	+0.7	0.90	0.81	-0.09	
A342111	Chronic nephritis, hypertension	3.4	3.8	+0.4	0.43	0.40	-0.03	
A342499	Nephritis, arteriosclerosis, hypertension	1.6	2.7	+1.1	0.77	0.54	-0.23	
A343065	Chronic nephritis	3.7	3.7	=0.0	0.39	0.53	+0.14	0.4 gm. caffein.*
A338719	Mild nephritis	3.2	2.8	-0.4	0.44	0.48	+0.04	Gout (?).
A341339	Chronic nephritis, hypertension	2.8	2.8	=0.0	0.57	0.65	+0.08	0.4 gm. caffein.*
A340860	Mild nephritis	2.4	2.3	-0.2	0.57	0.98	+0.41	
A341816	Chronic nephritis	2.5	2.8	+0.3	0.70	0.42	-0.28	Eighteen-hour specimen of urine.
A342534	Right kidney infected	2.0	2.4	+0.4	0.52	0.68	+0.16	
A343473	Mild nephritis	3.2	3.9	+0.7	0.62	0.36	-0.26	Eighteen-hour specimen of urine.

* Full dose is 0.8 gm. caffein.

the uric acid functional test; both investigations were conducted independently, and in no way were the results of the test used as a basis for the clinical investigation. For various reasons only thirty-seven of the cases, all unselected, were given complete tests as outlined. These were later grouped in Tables 9, 10 and 11, according to Conner's clinical diagnosis. A careful study of the protocols in the tables, however, will show that in three of the six cases in which a negative clinical diagnosis was made there was an elevation of blood uric acid following the administration of caffeine. Three of the patients were on active treatment for syphilis, and the question could easily be raised of whether they were not really suffering from temporary impairment of kidney function, not enough to produce clinical manifestations of kidney disease, but enough to hold back the uric acid. In two of the others the results were within the limits of experimental error. Theoretically, this uric acid test by the administration of caffeine, devised by Magath, should be ideal for an indication of early renal lesions. And it would seem to us to be worthy of further trial as a functional test. It is obviously unsuited to the needs of the life insurance examiner, as it would necessitate the observation of the patient for at least a full twenty-four-hour period.

MACLEAN AND DE WESSELOW UREA CONCENTRATION TEST

A functional test, similar to Magath's, has been suggested, however, which might be made suitable for life insurance examination. We refer to the determination of the amount of urea excreted when the blood is supersaturated with a large amount of urea given by mouth. The principles of this test have been suggested by several men. In 1914, McCaskey devised a very efficient urea concentration test and reported his findings in a series of observations. In 1917, the discussion of urea concentration was admirably brought out by Addis. He stated that the ideal testing substance would be a urinary constituent which is a true end product, incapable of changing in the body, and whose path of excretion is solely through the kidney. Urea, to a remarkable degree, fulfils these requirements. It is also rapidly absorbed from the stomach, so that its ingestion is immediately followed by a marked concentration in the blood. Moreover, we know what part of the kidney is directly involved in concentrating the urea from the blood, namely, the proximal convoluted tubules. Addis

made some very complete studies with Ambard's coefficient after feeding his patients with from 20 to 40 gm. of urea at the beginning of each day. This procedure would be impossible in connection with a life insurance examination. MacLean and de Wesselow have recently published their urea concentration test which has been further simplified by MacLean and Russell, giving us a technic that is easily applicable in any urinalysis laboratory. It necessitates the personal observation of the patient for a period of only two hours and requires only urea as the test substance, and some method of determining the amount of urea in the voided specimen. MacLean and his co-workers have now a total of more than 3,000 cases in which they have used this urea concentration test, and they report most enthusiastically on its applicability. Theoretically, they claim that it is preferable to any of the dye methods for testing kidney function, inasmuch as extraneous substances, such as dyes, may be passed by the normal portion of a kidney damaged in other portions. On the other hand, a kidney damaged only in certain portions, suddenly overloaded with urea, fails to excrete a normal amount of this substance in two hours. In this country a report by Weiss has just appeared, which in a limited way confirmed the value of the urea concentration test as a functional procedure. We have made a preliminary trial of the method, and have found that it is indeed a simple test, as far as its application is concerned (Table 12), and we believe that it is worthy of careful trial. The technic briefly is as follows:

The patient empties his bladder and is then given 15 gm. of urea. MacLean and de Wesselow dissolve the urea in 100 c.c. of water, flavored with tincture of orange. We have slightly modified this part of the procedure by dissolving the 15 gm. of urea in 80 c.c. of water, and after the administration of this small amount of fluid allowed the patient to drink 70 c.c. of water flavored with compound syrup of sarsaparilla. The patient must take no fluid during the next two-hour period. At the end of one hour a sample of urine is collected. At the end of the two hours another sample is collected. According to the more recent technic of MacLean and Russell, if the first sample is less than 150 c.c., only the second sample of urine need be tested for urea. Because of the diuretic effect of urea on some patients, if the first sample contains more than 150 c.c., urine must be collected for the third hour. In our laboratory we have used a modification of Marshall's urease method for the determination of the amount of urea, using 0.5 c.c.

TABLE 12
UREA CONCENTRATION TESTS

Case.	Blood urea, mg. per 100 c.c.	Intravenous phenol- sulphone- phthalein, per cent.	Urine urea, two-hour specimen.	Diagnosis.
A346518	50	45	3.1	Postherpetic neuralgia. No nephritis.
A346467	22	65	3.0	Cholecystitis. No nephritis.
A346624	32	55	2.92	Carcinoma of uterus. No nephritis.
A346914	22	55	3.38	Active pulmonary tuberculosis. No nephritis.
A346926	42	50	2.60	Stone in right ureter. Right ureterolithotomy.
A347185	50	60	4.0	Migraine, vertigo; arteriosclerosis. Slight hypertension.
A347183	..	55	3.08	Dysmenorrhea, trachoma. No nephritis.
A347350	20	60	3.32	Spina bifida.
A348281	40	65	4.12	Hypertension. Systolic blood pressure 192, diastolic 120. Cardiac case. No nephritis.
A348933	40	65	2.28	Hypertrophied prostate. Systolic blood pressure 142, diastolic 80.
A347960	..	60	3.4	Cholecystitis, with stones.
A348239	..	60	3.18	Sinus tachycardia. Systolic blood pressure 136, diastolic 96.
A348184	..	65	2.67	Gastric neurosis. Arteriosclerosis. Systolic blood pressure 124, diastolic 78.
A348283	..	65	3.3	Dermatitis. History of nephritis seventeen years ago. No evidence of nephritis.
A346641	44	45	1.88	Bilateral polycystic kidney.
A348017	38	65	1.9	Obesity (history incomplete). Systolic blood pressure 158, diastolic 100.
A347009	96	20	1.2	Nephrolithiasis? Chronic nephritis. Hypertension. Systolic blood pressure 214, diastolic 122.
A348004	..	30	1.08	Cardiovascular-renal syndrome. Systolic blood pressure 260, diastolic 160. (Albumin 3.)
A91999	..	20	0.96	Former tubercular epididymitis. Bilateral tuberculous kidneys (?) (Albumin 3.)

for the determination of the urea, and 5 c.c. for the determination of ammonia by Folin's method. MacLean and de Wesselow have recommended that the test be carried out by means of the hypobromite method. Weiss, however, believes that accurate results would not be obtained except by using the urease method for the determination of urea. MacLean has placed concentration of anything above 2 per cent as normal. In other words, if the percentage of urea in the urine voided at the end of two hours falls below 2, the kidney tissue is considered to be damaged. MacLean and de Wesselow were concerned chiefly in the study of the relation of transitory albuminuria, such as

is seen in soldiers to nephritis. Incidentally, they consider by far the best reagent for albumin to be sulfosalicylic acid, and by far the best for the determination of the significance of albumin to be the urea concentration test.

The life insurance examiner, it seems to us, must consider the significance of slight albuminuria much in the light as does the clinician, in spite of the differences under which the examination of the patient is carried on. As it would be obviously impracticable for a life insurance examination to contain all of the features of a thorough clinical and laboratory examination, those tests which are most easily handled are of necessity to be advised. We would suggest, as a problem in the future for the life insurance examiner, the determination of the feasibility of widening the scope of the examination to introduce some of the newer blood chemistry methods, in particular, blood urea and blood sugar determinations, and some functional test, even of more value, because of its ease of application, such as the urea concentration test for the determination of the significance of albuminuria in connection with the question of renal function.

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PRIMARY PAPILLARY EPITHELIOMA OF THE URETER: REVIEW OF THE LITERATURE AND REPORT OF A CASE *

E. STARR JUDD AND JOHN E. STRUTHERS

The diagnosis of primary papillomas of the ureter can be made in a certain number of instances. Zironi, Chevassu and Mock, Finsterer, Albarran (two cases), and Heresco made correct diagnoses. Probable ureteral neoplasm was diagnosed by Vorpahl, Richter, Paschkis, and Chiari, and the diagnosis was confirmed at operation or necropsy. Metcalf and Safford diagnosed their case ureteral calculus. In all the remaining cases reported the diagnosis was either made at operation or at necropsy (Wising and Blix, Voelcker, Hektoen, Rundle, Minich, Gerstein, Adler, Israel and Loewenstein, Suter, Butler, Spiess, and Schmitt).

The first reported case of primary papilloma of the ureter was probably that of Wising and Blix in 1878. They made a diagnosis of tumor of the rectum in a woman aged forty-one. At necropsy they found a medullary carcinoma involving the upper part of the ureter as far as the kidney. There was metastasis to the colon, mesentery of the colon, peritoneum, and liver.

Albarran, in 1896, probably was the first to diagnose a case correctly before operation or necropsy. His diagnosis was confirmed at operation. This case was reported in 1899. In 1902, he reported a case correctly diagnosed as proved by operation. In this paper he refers to another case which had been correctly diagnosed by Heresco, one of his pupils.

Etiology.—In the twenty-five cases reported in the literature calculi were given as the probable cause in six. In two of these, however, there was no evidence of calculi. Thus calculi as the etiologic factor could be considered in but 16 per cent.

Vorpahl quotes Uliszewski, referring to the connection between carcinoma of the urinary tract and the formation of calculi. That

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the action of the calculi is considered is evident, because the large majority of carcinomas of the gallbladder occur with cholelithiasis, and, besides, primary carcinoma of the bile passages gives rise to small strictures of about the same extent as that of local inflammation resulting from impaction of a calculus. Similar results might occur in the urinary passages.

The tumors usually occur between the ages of forty and sixty. The parts of the urinary tract above the bladder where stones are retained are the renal pelvis, the commencement of the ureter, and its portion above the bladder where the lumen becomes narrowed. In cases in which the primary growths are found at these points, and in which there are calculi, it is probable that the development of the tumor may be traced to pressure irritation from the calculi.

Certain writers consider leukoplakia as a probable origin of both the benign and the malignant neoplasms (Zironi). The surfaces of the pelvis of the kidney and the ureter are covered by stratified squamous epithelium, which, in inflammatory processes, either simple or chronic, may give origin to calculi or tuberculosis in the urinary passages, or which, in its superficial planes, may be transformed into epithelium with numerous stratifications, while the mucosa is markedly infiltrated with round cells and consequently becomes sclerous. When this occurs it is spoken of as leukoplakia, and it is on these areas that benign and malignant neoplasms easily develop. Pathologically the growths in the renal pelvis and in the ureters are:

1. Epithelial growths (a) papilloma; (b) papillary epithelioma; (c) epithelioma (nonpapillary).
2. Mesodermal growths.
3. Adenocarcinomas.

In the twenty-five reported cases carcinoma seemed to predominate in proportion of two to one. The findings were:

Adenocarcinoma and medullary carcinoma, 17.

Papillary and simple epithelioma, 8.

Two cases of mesodermal growths are referred to as involving the ureter, the case of Targett, which invaded the right ureter from its origin on the posterior wall of the abdomen, and the case of Willutski, of an alveolar sarcoma of the left ureter in a man aged twenty-five. Both were secondary growths.

Albarran collected ten cases of ureteral neoplasms, five were papillomas, three papillary epitheliomas, and two nonpapillary epitheliomas.

Of the twenty-five patients in the collected series, fifteen were operated on, with recoveries in eight. The time after operation was too short, however, definitely to determine the final prognosis with regard to recovery or metastasis. One patient operated on by Albarran committed suicide four years after the operation. He had been cystoscoped one month before, and no recurrence was observed in the bladder or ureter.

Hydronephrosis was definitely stated to be present in ten patients (40 per cent). In the patient of Davy and Richter the description of the ureteral obstruction was indicative of hydronephrosis, but it was not definitely stated that it was present.

Symptoms.—The principal symptoms are hematuria, swelling, and pain, the same as with tumor of the kidney. The hematuria is usually the first symptom and may not be associated with pain. It generally comes on without cause; the blood is profuse and thoroughly mixed with the urine. If there is clot formation the pain may be intense and colicky in character. Usually there is a vesical disturbance, evidenced by frequent micturition. The ureteral clots passed under these circumstances are very characteristic. They have the appearance of angleworms and sometimes are of great length. In our own case the clot was sufficiently hard to make the patient think he had passed a stone. The bleeding may be intermittent and may extend over months or years.

Von Capellen performed a nephrectomy in his case. Weeks later, after the patient was up and feeling well, she had a sharp hemorrhage unaccompanied by pain. The author states that it was clear that the ureter had not healed and that the hemorrhage came from a tumor or hemorrhagic inflammation. A second operation proved the growth to be a primary carcinoma of the ureter; it was removed.

Suter believed that his patient had a so-called essential hemorrhage. Before his final diagnosis he had performed cystotomy, nephrotomy, nephrectomy, and finally ureterectomy, at which time the growth which proved to be a primary papilloma was removed with the ureter.

Albarran's case demonstrates that one may be led astray by palpation of a mass. At cystoscopic examination he discovered, projecting from the left ureteral orifice, a small tumor 2.5 by 1.5 cm. It appeared to be implanted on the vesical wall by a large base. Its surface was mamillated, but not papillary, giving the appearance of an epithelioma.

On combined vaginal and abdominal examination he felt in the left lateral culdesac placed up against the uterus, which had preserved its mobility, an indurated mass with indefinite borders. He believed it to be the mass observed through the cystoscope. Operation showed an old salpingo-oöphoritis. He closed the peritoneum after removing this mass, prolonged the abdominal incision, and exposed and opened the ureter and bladder. Here the tumor seen on cystoscopic examination was observed implanted by a thin pedicle on the posterior ureteral wall near the bladder.

Pain may or may not be present in these cases. It may be a dull ache or colicky, especially if the ureter becomes occluded by a clot. Pain occurred as the chief symptom, probably in one-third of the cases, and in the majority of cases it was noted as the principal symptom some time during the course of the disease.

The urine may contain red blood cells, ureteral epithelium, atypical cells, and fragments of tumor. Later, if infection takes place, pus will also be present, and pyelonephritis or pyonephrosis with elevation of temperature develops. The kidney may become large and palpable.

Cystoscopic examination.—The bladder and the ureteral orifices may appear normal, or there may be an inflammatory reaction around the meatus, manifested by a ring of edema or local redness with or without erosion around the orifice or distortion of the orifice. Or, because of an infected hydronephrosis, there may be an associated infection in the bladder. The ureteral orifice on the side of the growth may not be discernible, and in its place, if the growth is low in the ureter, a bulging may be observed. If obstruction from the growth is complete, the kidney on that side will be functionless. Again, when partially obstructed, blood or turbid urine may be seen coming from the orifice. On passing the ureteral catheter an obstruction may be encountered where normally there should be none. If the obstruction is partial, blood may flow from the catheter, and after passing the obstruction there may be a flow of turbid urine from an infected hydronephrotic kidney or, if not infected, clear urine.

Treatment.—The treatment of a growth affecting the lower part of the ureter depends on its extent. Marion is enthusiastic over his success in destroying with the electric current polyps in the ureter in two cases. The pain and discomfort were not greater than that experienced in destroying polyps of the bladder in the same patients. In cases in which the lower end of the ureter is involved without enlarge-

ment of the kidney the line of procedure depends on the extent of the lesion. Albarran believes that when the portion of the ureter situated above the growth is apparently all right, and at the same time the kidney is functionally useful, it appears logical to extirpate the tumor and perform a ureteroneocystostomy, or, if this operation is impossible, to anastomose the ureter into the intestines.

In cases in which the growth is low the ureter should be catheterized during operation to make sure there is no growth higher. The multiplicity in villous tumors is particularly to be feared. It is not unusual to see tumors of the pelvis grafting themselves into the inferior part of the ureter, or even into the bladder near the ureteral orifice. Similar grafts do not usually occur in nonvillous neoplasms.

In another group of cases the growths do not project into the bladder, but cause induration of the ureter, which, however, preserves its rounded form. A portion of the bladder wall is often invaded. Albarran practices extirpation of the tumor from within out, uniting the section of the ureter to the bladder. If there is peri-ureteral inflammation the possibilities are that the intravesical passage is insufficient and the ureter should be transplanted outside the bladder.

The ureteral obstruction due to the neoplasm resulted in hydronephrosis in 40 per cent of the reported cases. Many patients with pyelitis have a resultant pyonephrosis with destruction of the adjoining kidney tissue. In such cases nephrectomy and ureterectomy should be performed.

The immediate results of operation for simple papilloma are good. There is always, however, grave danger of recurrence of the disease, either immediately or within a few months or several years after operation.

REPORT OF CASE

Case A344470. Mr. T. E. C., aged forty-eight years, was examined in the Clinic December 27, 1920. His tonsils had been removed when he was eighteen. He had had influenza in 1890 and 1918. Gonorrhea had been contracted in 1905; cystoscopic examinations had been made six times in the past two years. Two years before he had begun to pass bloody urine and had had pain in the head of the penis at the end of urination. Attacks of hematuria occurred every four to seven days and lasted two days with pain. There were intervals when the remissions were longer, but these were few. At times he passed considerable blood and at times it was just noticeable. Pain remained about the same throughout the two years; sometimes it was referred to the suprapubic area; it had not been severe until seventeen days before, when it became acute in the bladder and penis and he passed what he thought was a dark stone 1.25 cm. long and 1.87 cm. thick. Eight days later he had acute retention lasting two hours, associated with con-

siderable pain. For the past six months there had rarely been a day that the urine had been free from blood. He had been told, following one of his cystoscopic examinations, that he had an obstruction of some kind in his left ureter. Roentgen-ray examinations had been negative.

The patient was 5 feet and 5 inches in height and weighed 137 pounds, which is his average. Infected tonsils were graded 2, with plugs. The septum was deflected to the left. The roentgen ray showed five teeth with periapical infection. The systolic blood pressure was 118, the diastolic 50. The pulse rate was 90, the temperature was 98. The Wassermann reaction was negative. The urinalysis was negative except for an occasional red blood cell and pus 1, fifteen cells were counted in the field. The combined phenol-



FIG. 99.—Extensive pyonephrosis. Large abscess cavities which were filled with pus. The kidney weighed 120 gm.

sulphonaphthalein test, 300 c.c. gave 50 per cent return in two hours and fifteen minutes. The roentgen-ray examination of the urinary tract was negative.

Cystoscopic examination revealed left hematuria with obstruction at the opening with a neoplasm protruding, which made it impossible to introduce the catheter. Secretion was not apparent, but the growth bled easily on contact. The right kidney was normal.

A diagnosis was made of left ureteral neoplasm with a possible primary left renal neoplasm, and exploration of the left kidney and left lower ureter was recommended.

January 10, 1921, a left nephrectomy was performed for evident pyonephrosis. Eighty per cent of the substance of the kidney was found to be destroyed. The kid-

ney weighed 120 gm. and was full of pus (Fig. 99). Partial subcapsular nephrectomy was performed, the ureter was ligated and dropped back, with the recommendation that the ureter and a piece of the wall of the bladder be removed later when the patient's condition would permit.

January 21, 1921, a left ureterectomy with resection of an area 3.5 by 2.5 cm. of the wall of the bladder was performed, through an anterior extraperitoneal incision. A definite papillary epithelioma, 8 cm. in diameter, involving the lower ureter, was found. The ureter was about 3 cm. in diameter throughout its entire course (Fig. 100).

The pathologic report shows marked pyonephrosis with multiple large cortical abscesses and extensive destruction of the substance of the kidney. The pelvis of the kidney was dilated and thick walled, but entirely smooth throughout. The ureter measured 20 cm. in length and 3 cm. in diameter. On opening the ureter the lower 8 cm. was found

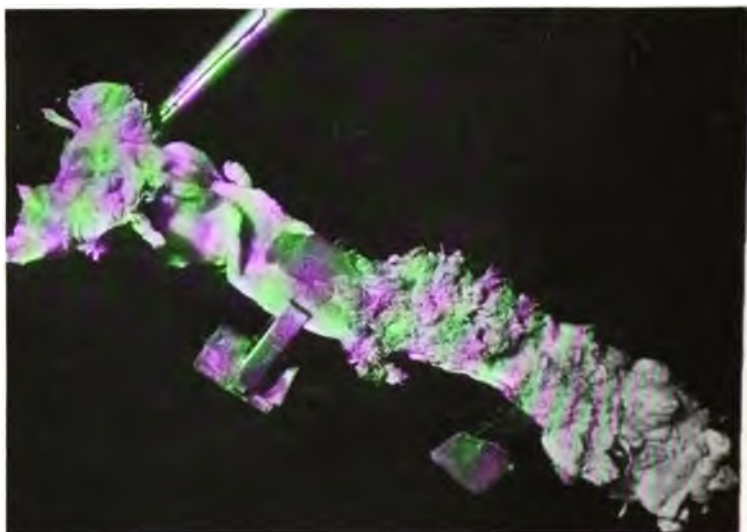


FIG. 100.—Right ureter with small portion of the vesical wall. A definite papillary epithelioma 8 cm. in diameter involves the lower portion of the ureter.

completely filled with a shaggy granular partially necrotic papillary growth which covered the entire surface of the ureter. A section of this area revealed typical papillary epithelioma. Mitotic figures were strikingly noticeable in all the fields and the individual cells showed very little differentiation.

The patient was dismissed February 21, 1920, with the wounds healed and in good condition.

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VESICAL CALCULUS*

JOHN L. CRENSHAW

Recent literature on vesical calculi contains many reports of large or peculiar stones, complications, and choice of operation. There are, however, only three articles in which a large number of cases are reported, namely, Barney reporting 455 cases from the Massachusetts General Hospital; Thomson reporting 2,962 from Canton, China, and Assendelft reporting a collection of 630 cases from several Russian hospitals.

The data of this article are based on a study of the records of 621 patients with vesical calculus examined at the Mayo Clinic between June 1, 1907 and April 1, 1921, approximately fourteen years.

GENERAL CONSIDERATIONS

The cases have been divided into two groups: (1) patients with ureteral-bladder stones, or those who had histories of kidney colic and who on our examination had a stone of ureteral origin without accretion in the bladder, removed from the bladder, and (2) true bladder stones, or those which had formed entirely or partially in the bladder.

Fifteen patients had ureteral-bladder stones; thirteen were men and two were women; the oldest was seventy-one, the youngest twenty-two; the average age was forty-five and one-tenth years.

Litholapaxy was performed in five; the stone was removed with a specimen taken through the cystoscope in six; it was passed following cystoscopy in three, and in one it was not removed.

There was no mortality in this group, and no further data concerning it are considered in this paper, all percentages being based on 606 cases, or constituent groups of the true bladder stone.

Of the 606 patients with stone in the bladder, 577 (95.21 per cent) were males, and twenty-nine (4.78 per cent) were females. The oldest was eighty-six, the youngest four; the average age was fifty-five and fifty-nine hundredths years.

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TABLE 1
AGES BY DECADES

	Number.	Per cent.
From 1 to 10.....	4	0.66
From 11 to 20.....	13	2.14
From 21 to 30.....	34	5.61
From 31 to 40.....	59	9.73
From 41 to 50.....	71	11.71
From 51 to 60.....	164	27.06
From 61 to 70.....	183	30.19
From 71 to 80.....	69	11.38
From 81 to 90.....	9	1.48

TABLE 2
SEX, AGE,* AND METHOD OF REMOVAL

Method of removal.	Cases.	Male.		Female.		Oldest, years.	Youngest, years.	Average age, years.
		Number.	Per cent.	Number.	Per cent.			
Lithotrixy.....	153	138	90.19	15	9.8	79	16	49.05
Suprapubic.....	395	385	97.46	10	2.53	86	4	58.1
Through the cystoscope.....	14	11	78.57	3	21.42	74	28	48.5
Perineal.....	14	14	100	..	..	81	43	67.0
Through the urethra with forceps.....	1	..	..	1	100	7	7	7.0
Not removed.....	29	29	100	..	..	79	22	52.79

* The average duration of symptoms was five and eighty-six hundredths years. The age of the patients at the onset of symptoms was: the oldest, eighty-one; the youngest, one; the average was forty-nine and fifty-two hundredths years.

It is of interest that the decade of highest incidence (30.19 per cent) was between sixty-one and seventy, while between fifty-one and seventy-one, incidence was 57.25 per cent. Seventy and eleven hundredths per cent of the patients were more than fifty. Thomson reports that 43 per cent occurred under the age of twenty, and 84 per cent were under fifty-one. Assendelft reports 92 per cent of 630 patients under thirty; Barney reports 67 per cent between fifty and eighty years, practically the same incidence as in our series. Only four (0.66 per cent) were under ten, which is in striking contrast to 25 per cent of Thomson's series, and the 77 per cent under ten in Assendelft's series. Suñer reports forty cases of bladder stone in children. Cahill states that in the children's surgical service in Bellevue Hospital no bladder calculi were reported

until 1920, when there were three cases in patients of two, nine, and three years. Cahill also states that the reports of the Post-Graduate Hospital, New York, show less than 2 per cent of bladder stone in children. In our four cases, three of the stones were removed by suprapubic cystostomy, and one with forceps through the urethra.

The diagnosis of bladder stone by means of a "feeler" has been discarded by most urologists in favor of the roentgen ray and the cystoscope. The accuracy of these methods is shown in Table 3.

TABLE 3
DIAGNOSIS BY ROENTGEN RAY AND CYSTOSCOPE

	Patients examined.		Positive.		Negative.		Indeterminate.	
	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.
Roentgen ray	449	74.09	345	76.83	91	20.26	13	2.89
Cystoscope	459	75.74	445	96.94	10	2.17	4	0.87

The high percentage of positive diagnoses with the cystoscope (96.94 per cent) must be explained by the fact that the cystoscopist usually had the benefit of seeing the plates before cystoscopy; also in some instances, when poor plates were reported "negative" and a request made for a reray, the stone was discovered by cystoscopy and the reray was not made.

Of 606 cases, there were nineteen (3.13 per cent) undiagnosed and discovered at operation. The diagnostic analysis of these nineteen cases is given in Table 4.

TABLE 4
DIAGNOSTIC ANALYSIS OF NINETEEN CASES

	Cases.
Negative roentgen-ray report	6
No roentgen-ray report	13
Negative cystoscopic report	3
No cystoscopic report	16
Operated on for prostatic hypertrophy	17
Operated on for stricture	2

The three patients in whom cystoscopic examination for stone was negative had large hypertrophied prostates and one had a cicatricial

posterior urethra also. All had trabeculated bladders and many cellules. Two had two small stones each, and one had one small stone. We may, therefore, estimate the efficiency of a combined roentgen-ray and cystoscopic examination for bladder stone at 96.87 per cent. Additional lesions discovered by cystoscopy are given in Table 5.

TABLE 5
ADDITIONAL LESIONS DISCOVERED BY CYSTOSCOPY

	Number.	Per cent.
Patients cystoscoped.....	459	75.74 of 606
Patients not cystoscoped.....	147	24.25 of 606
Patients with cystitis.....	400	87.14
Patients with prostatic enlargement.....	277	60.34
		45.7 of 606
Patients with trabeculation.....	118	25.7
Patients with stricture of the urethra.....	45	9.8
Patients with deformity of the bladder.....	24	5.22
Patients with diverticulum.....	21	4.57
Patients with tumor of the bladder.....	15	3.26
Patients with atony of the bladder.....	11	2.39
Patients with tuberculosis of the kidney.....	1	0.217

Items of interest in these findings are:

1. Stone occurred in a tuberculous bladder in only one patient. Stone in the bladder and tuberculosis of the bladder certainly rarely coexist, owing probably to the fact that urinary tuberculosis usually occurs before prostatic age, and that the severity of the cystitis prevents retention. There was a stricture of the urethra in this case, which probably explains the stone formation.

2. Prostatic obstruction was present in 277 cases and urethral stricture in forty-five, or a total of 322 cases (70.14 per cent) with urethral obstruction.

3. In twenty-one patients a diverticulum of the bladder was found on cystoscopy; in twelve others it was found at operation, making a total of thirty-three (5.44 per cent) who had diverticula which seemed to be a causative factor in the formation of stone. In seventeen of these there was stone in the bladder alone; in six stone in the diverticulum alone, and in ten stones in both diverticulum and bladder. During this period there were 226 patients with diverticula of the bladder, or an incidence of 14.6 per cent of stone in the cases of diverticula.

4. Fifteen patients had stone and tumor in the bladder; two of

these also had diverticula, the growth being in the diverticulum in one and just outside it in another.

Two hundred and twenty-eight patients had an average of 4.3 ounces of residual urine, and in twenty-six the residue was questionable. Some of the patients who had prostatic hypertrophy and stone in the bladder emptied the bladder completely so long as the stone remained in the bladder, but required prostatectomy for retention after its removal. On the other hand, there was sometimes an inflammatory enlargement of the prostate causing retention which subsided entirely after the removal of the stone. In many cases in which a diverticulum was present and no retained urine was obtainable by catheter from the bladder, a cystogram made after voiding the medium showed the bladder to be empty, but retention in the diverticulum.

The literature, both ancient and recent, is crowded with reports of large or unusual bladder stones. Apparently the largest authentic stone on record is that reported recently by Randall, which weighed 64 ounces when removed, and 54 ounces after drying. Thirty-eight and one-half ounces seems to be the largest stone removed with recovery of the patient (Smith). Osgood reports from the literature fifty cases of large stone, twenty from necropsy and thirty in which operation was performed; the mortality in the latter was 50 per cent. Necropsy reports show several stones weighing as much as 51 ounces.

The largest stone in our series was 6.5 by 5 cm. This seems relatively small in view of the fact that the average duration of symptoms was five and eighty-six hundredths years. However, there is undoubtedly a great variation in the growth of stones, and time is only a minor factor. Hijmans reports eleven large stones weighing 110 gm. found in the bladder six years after cystostomy. Hunner found a stone that had formed in two or three weeks around a piece of rubber drain. In one of our patients a well-defined stone had formed around a catheter head in four weeks.

Of the 577 patients operated on, 386 had a single stone. The diameters were 1 cm. or less in sixty-seven; 2 cm. in 122; 3 cm. in 114; 4 cm. in forty-eight, and 5 cm. or more in ten. The size was not mentioned in twenty-five. One hundred and ninety had multiple stones; seventy-two had two stones; twenty-six had three stones; eight had four stones, and eighty-four had five or more. There was one pseudostone.

Stone in other portions of the urinary tract coexistent with the stones in the bladder occurred as indicated in Table 6.

TABLE 6

OCCURRENCE OF STONE IN OTHER PORTIONS OF THE URINARY TRACT COEXISTENT WITH STONE IN THE BLADDER

	Positive.		Questionable.	
	Number.	Per cent.	Number.	Per cent.
Renal lithiasis.....	14	2.31	12	1.98
[reteral stones.....	6	0.99	8	1.32
Prostatic stones.....	8	1.32	2	0.33
[rethral stones.....	1	0.16		

A severe renal colic, even several times repeated, is often forgotten by the patient with bladder stone as soon as the kidney stone passes into the bladder, particularly if several years have elapsed between the cessation of the colics and the onset of bladder symptoms, since the average patient sees no connection between the two and does not mention the kidney symptoms unless he is questioned. It is necessary, therefore, on finding a bladder stone, to question each patient in detail with regard to previous pain in the region of the kidney. Such data have been carefully elicited in the majority of our histories.

TABLE 7

PREVIOUS RENAL LITHIASIS

	Cases.	Per cent.
Renal colic, positive.....	101	16.66
Renal colic, questionable.....	9	1.48
Stones passed.....	40	39.6 of 101
Stones not passed.....	60	59.4 of 101
Operations on the kidney.....	6	0.99

It is of interest that, in spite of severe cystitis in most cases, histories of chills, fever, and sweats were recorded in only forty-one (6.76 per cent), and in at least sixteen of these there was coexisting pyelonephritis, leaving twenty-five (4.12 per cent) in which the bladder or urethra might be the focus. This low percentage and the low percentage of metastasis in cases of tumor of the bladder seem to corroborate the fact that the bladder has a relatively poor lymphatic supply. The presence of chills, fever, and sweats in a given case should, therefore, suggest an extension of the infection to other organs than the bladder.

An effort was made from all the data recorded in each case in the

series to establish the probable source of the stone, whether bladder, kidney or urethra, and, if vesical, to establish the principal cause. The results of these analyses are shown in Table 8.

TABLE 8
PROBABLE SOURCE OR CAUSE OF STONES IN THE BLADDER

	Retention from					Cystitis.	Foreign body.	Diverticulum of the bladder.	Kidney.	Urethra (prostatic).	Congenital deformity.	Pseudostones.	Indeterminate.
	Prostate.	Stricture.	Atony.	Deformity of the bladder.	Cystitis.								
Lithotripsy.....	36	12	3	2	..	42	4	5	45	2	..	1	1
Through cystoscope.....	..	2	..	..	..	3	2	1	6	..	..	..	..
Through urethra.....	..	..	..	..	..	..	1	..	..	..	..	..	..
Suprapubic cystostomy.....	204	20	6	1	5	58	14	24	45	4	1	..	17
Perineal cystostomy.....	11	2	..	..	..	1	..	..	5	..	..	..	..
Stones not removed.....	15	2	..	..	..	2	..	3	..	..	..	..	2
Total.....	266	38	10	3	3	105	21	33	99	6	1	1	20
Per cent.....	45.89	6.27	1.65	0.49	0.49	17.32	5.46	5.44	16.33	0.99	0.16	0.16	3.3

Cystitis was given as the cause rather than the result of stone only when there was apparently no other reason for the formation.

Numerous cases have been reported in which foreign bodies of various types were the nucleus of bladder stones, and instances of their remaining in the bladder for as long as seventeen years without symptoms have been noted.^{3, 5, 10, 12, 13} Foreign bodies were demonstrated to be the nucleus in twenty-one (3.46 per cent) of our series.

TABLE 9
TWENTY-ONE CASES* (3.46 PER CENT) OF STONE WITH FOREIGN BODY NUCLEUS IN THE BLADDER OF MALES

	Cases.	Per cent.
Lithotripsy:		
Rubber tissue.....	3	14.28
Silk sutures.....	2	9.52
Catheter head.....	1	4.76
Surgical:		
Hairpin.....	4	19.4
Suture.....	3	14.28
Gauze.....	3	14.28
Suture and curved needle.....	1	4.76
Catheter head.....	1	4.76
Knife-blade.....	1	4.76
Part of LaForte guide.....	1	4.76
Piece of bone from fracture of pubis.....	1	4.76

* Seven of these cases have been reported by Judd.

TABLE 10

CAUSE OF TWENTY-NINE CASES (4.78 PER CENT) OF STONE IN THE BLADDER OF FEMALES

	Cases.	Per cent.
Probable source of stone:		
Cystitis	9	31.03
Foreign body	8	27.58
Kidney	8	27.58
Diverticulum	2	6.89
Atony	1	3.44
Pseudostone, flint	1	3.44
Foreign body:		
Hairpin	4	
Catheter head	2	
Silk suture	1	
Rubber tissue	1	

TABLE 11

METHODS OF REMOVAL OF STONES IN THE BLADDER: RESULTS

	Ether.		Gas.		Local.		Sacral.		Anesthetic not stated.		Total.	
	Num-ber.	Per-cent.	Num-ber.	Per-cent.	Num-ber.	Per-cent.	Num-ber.	Per-cent.	Num-ber.	Per-cent.	Num-ber.	Per-cent.
Lithotripsy:												
Patients	38	24.83	..	..	115	75.16	..	..	..	..	153	25.94
Average days in hospital ..	4.41	..	..	..	1	..	..	..	..	..	4.2	..
Mortality	1	..	..	..	1	..	..	..	..	..	2	1.3
Average number of days of life after operation	16	..	..	..	8	..	..	..	..	..	9.5	..
Recurrences (first)	4	33.3	..	..	8	66.6	..	..	..	..	12	7.64
Through cystoscope:												
Patients	2	14.28	..	..	12	87.71	..	..	..	..	14	2.31
Average days in hospital ..	4	..	..	..	..	..	..	..	..	..	4	..
Mortality	..	..	..	..	..	..	..	..	..	..	..	..
Recurrences (first)	..	..	..	..	1	..	..	..	..	..	1	7.14
Through urethra:												
Patients	1	..	..	..	..	..	..	..	..	..	1	0.16
Average days in hospital ..	2	..	..	..	..	..	..	..	..	..	2	..
Mortality	..	..	..	..	..	..	..	..	..	..	..	..
Recurrences (first)	..	..	..	..	..	..	..	..	..	..	..	..
Suprapubic cystostomy:												
Patients	372	94.17	1	0.25	6	1.51	8	0.75	18	8.29	395	65.18
Average days in hospital ..	14.02	..	37	..	27.83	..	10.3	..	14	..	14.27	..
Mortality	31	..	..	..	8	..	..	..	..	..	34	8.6
Average number of days of life after operation	15.5	..	..	..	12.3	..	..	..	..	..	14.7	..
Recurrences (first)	18	..	..	..	..	..	..	..	..	..	18	4.65
Perineal cystostomy:												
Patients	11	78.57	..	..	..	..	..	..	8	21.42	14	2.31
Average days in hospital ..	11.54	..	..	..	..	..	..	..	45	..	14.85	..
Mortality	..	..	..	..	..	..	..	..	..	..	..	..
Recurrences (first)	1	..	..	..	..	..	..	..	..	..	1	7.14

Stone in the bladder in the female is a comparatively rare occurrence; hence the causes are of interest. I have tabulated under the name "pseudostone" a stone 2 by 1 cm. which I attempted to crush with a lithotrite; as I was unable to break the stone, it was removed whole

through the urethra. Examination showed it to be a piece of flint which the patient later confessed having passed into the bladder.

Twenty-nine of 606 patients had positive diagnoses of stone and were not operated on, and 577 had single or multiple stones removed (Table 11).

That the mortality was approximately the same with or without an associated operation is partially explained by the fact that such operations were performed only in the better surgical risks. Only the stones were removed in the bad risks, and other operations were deferred until conditions were more favorable (Tables 12 and 13).

TABLE 12

ONE HUNDRED AND FIFTY ASSOCIATED OPERATIONS IN 147 CASES (35.85 PER CENT OF 409 CASES) IN WHICH THE OPERATION PERFORMED WAS SUPRAPUBIC OR PERINEAL CYSTOSTOMY

Associated operations at the time the stone was removed.	Operations.	Per cent.
Suprapubic prostatectomy.....	104	25.42
Perineal prostatectomy.....	14	3.42
Excision of diverticulum.....	5	1.22
Dilatation of stricture.....	7	1.17
Cautery excision of carcinoma of the bladder.....	4	0.97
Resection of carcinoma of the bladder.....	2	0.48
Removal of specimen from the bladder for diagnosis.....	2	0.48
Removal of specimen from the prostate for diagnosis.....	1	0.24
Herniotomy.....	3	0.73
Closure of perineal fistula.....	3	0.73
Excision of suprapubic sinus.....	2	0.48
Excision of lipoma of groin.....	1	0.24
Closure of vesico-intestinal and abdominal-intestinal fistula....	1	0.24
Cholecystostomy.....	1	0.24

TABLE 13

MORTALITY*

	Patients	Per cent.
Without associated operations.....	430	74.52
Mortality.....	26	6.04
With associated operations.....	147	35.85
Mortality.....	10	6.8
With associated suprapubic prostatectomy.....	104	25.36
Mortality.....	7	6.7

* Five hundred seventy-seven patients were operated on. Thirty-six, or 6.23 per cent, died (5.79 per cent of the 621 patients).

RECURRING STONE

Stones do not occur in the bladder without cause, and it should be the surgeon's duty, if possible, to remove this cause as well as the stone itself. Recurrences may be due to failure to remove the original cause or to fragments or small stones left behind, or the cause may have developed subsequently to the removal of the original stone. If recurrences are to be avoided, precautions as follows must be taken:

1. Roentgen-ray and cystoscopic examinations must be made after the stone is removed, to make sure that no fragments of stone remain.
2. Infected kidneys should be cleared up with pelvic lavage and the removal of foci of infection.
3. Renal lithiasis, if present, should be removed.
4. Cystitis should be cleared up by lavage of the bladder and drainage, if necessary.
5. Causes of retention, such as enlarged prostate or stricture, should be removed; or, if the cause cannot be removed, as in cases of atonic bladder, the residual urine should be withdrawn regularly.
6. Diverticula, if they retain urine or cause cystitis, should be removed.
7. Hygienic and dietetic measures that benefit the general health should be adopted.

Twelve (7.84 per cent) of the recurrences followed litholapaxy; eighteen (4.55 per cent) followed suprapubic cystostomy; one (7.14 per cent) followed perineal cystostomy, and one (7.14 per cent) followed removal of the stone through the cystoscope: a total of thirty-two (5.54 per cent) in the 577 cases.

The causes of the original bladder stone and subsequent recurrences are shown in Table 14.

TABLE 14
TOTAL RECURRENCES (THIRTY-TWO CASES)

Source of original stone.	Cases.	Source of first recurrence.	Source of second recurrence.
Prostate.....	16	12	
Kidney.....	5	3	1
Cord bladder.....	4	3	1
Stricture.....	3	3	1
Cystitis.....	2	6	2
Tumor of bladder.....	1	1	
Diverticulum.....	1	2	1
Not given.....	..	1	
Left at former operation.....	..	1	

An analysis of the causes of recurrence in relation to previous surgery in these thirty-two cases is shown in Table 15. There were not more than two recurrences in any case.

TABLE 15
CAUSES OF RECURRENCE

	First recurrence.	Second recurrence.
Failure to remove cause of original stone (22)		
Prostate.....	9	
Kidney.....	3	1
Atonic bladder.....	3	1
Cystitis.....	3	
Diverticulum.....	1	1
Stricture.....	1	
Tumor.....	1	
Questionable.....	1	
Stone or fragments left at previous removal (perineal prosta- tectomy).....	1	
Cause of recurrence developed subsequently to removal of original stone.....	9	3
Total.....	32	6

CONCLUSIONS

1. The incidence in the United States of patients with stone in the bladder is greatly increased after the age of fifty, in contrast to some other countries where it is largely a disease of childhood and early adult life.

2. Combined roentgen-ray and cystoscopic diagnosis is accurate in approximately 96.87 per cent of the cases.

3. The incidence of diverticulum of the bladder is much greater than is usually believed, and stone in the bladder occurs in about 14 per cent of these cases.

4. The low mortality of litholapaxy and the ease with which it can be performed under caudal anesthesia should tend to increase the instances of stones being removed by this method. The advantages more than compensate for the very slight increase in recurrence.

5. Operations associated with that of removal of stone, in selected cases, do not materially increase the mortality.

6. The majority of recurrences could be avoided if precautions were taken to remove the cause of the original stone.

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COINCIDENT CALCULUS AND DIVERTICULUM OF THE BLADDER*

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It is not our purpose to discuss the much argued question of whether diverticula of the bladder are congenital or acquired, but to direct attention to the importance of diverticula in some cases as a factor in the formation of stone in the bladder. Recently a study was made of 609 patients with stone in the bladder who were examined or treated in the Mayo Clinic between the years 1907 and 1920 inclusive. During the same period there were 222 who had diverticula of the bladder of such size or shape as to make them of importance pathologically. Twenty-eight of the 222 patients (12.1 per cent) had diverticula and bladder stone. These diverticula did not include the small depressions commonly known as "cellules" which are found in most retention bladders. They varied in size from 2 or 3 cm. in diameter to large sacs holding many ounces, and in some instances they were larger than the bladder itself. The lateral walls and base were the most frequent areas of communication with the cavity of the bladder, although a few were found in which the opening was in the posterior wall or dome of the bladder. The incidence in women or young men was small, the majority occurring in men who were fifty years of age or more.

Pathology.—Before infection takes place diverticula consist of thin-walled sacs which may be lined with bladder mucosa or, as reported by Hinman, the mucosa may be entirely absent, the outer coats being greatly stretched bladder musculature, usually without any continuous well-defined muscle layers. At this stage they are but slightly attached to the perivesical tissues and often can be invaginated into the bladder. The stretching of the sac wall renders the musculature more or less atonic, and the atony as well as the fact that the mouth of the diverticulum is usually relatively small and located in the upper portion of the sac, favor retention of urine, although the main cavity of the bladder may empty completely. Retention in the sac soon leads to infection.

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with the result that the previously thin wall becomes greatly thickened with inflammatory infiltration, is friable, sometimes necrotic, and densely adherent to all surrounding tissues. The constant overflow of infected urine into the bladder produces a cystitis which may be of such severity that a satisfactory cystoscopy cannot be performed and the mouth of the diverticulum can be overlooked easily.

Formation of stone in the urinary tract is usually attributable to two known predisposing causes, retention and a nucleus for the deposit of urinary salts. Since both of these conditions exist for long periods without the formation of stone it seems to be evident that there are other factors that have not been proved definitely. It is readily understandable, however, that a diverticulum of the bladder, with retention, infection, and nuclei in the shape of blood-clots, desquamated epithelium, pus, necrotic tissue, and so forth, is a fertile field for the formation of stone. The stone may remain in the diverticulum or it may migrate into the main cavity of the bladder.

Symptoms.—The symptoms of diverticulum of the bladder and of stone in a diverticulum are alike and essentially those of the coexisting vesical infection, such as frequency, pain, and pyuria, so that a differential diagnosis cannot always be made without the aid of cystoscopy and the roentgen ray. A diverticulum can always be diagnosed if the possibility of its existence is recognized by the examiner, but since the coexisting cystitis, stone in the bladder, or hypertrophy of the prostate are often alone sufficient to account for the symptoms, the possibility of a diverticulum is often overlooked and the further necessary examinations are not made. It has been definitely shown also that a diverticulum can easily be overlooked by a competent surgeon performing a suprapubic cystostomy. There are several conditions, however, that should indicate the possibility of a diverticulum and lead to the examinations necessary for a positive diagnosis.

1. Hemorrhage from the bladder without other assignable cause, the hemorrhage being more profuse than is usual with cystitis or stone and probably the result of severe infection and stretching of the sac walls.

2. A marked slowness in emptying the bladder, the urine coming in a dribble, in the absence of an enlarged prostate, stricture, or lesion of the spinal cord. This symptom is found chiefly with diverticula of large capacity and easily dilatable walls, where the force of the bladder is directed along the line of least resistance into the diverticulum rather than into the urethra.

3. A very low phenolsulphonephthalein or indigocarmin output from a catheterized bladder, coincident with a normal or nearly normal blood urea, since a portion of the dye may be retained in a diverticulum.

4. Persistent infection or the reformation of stones in the bladder without assignable cause.

5. Shadows in the roentgenograms suggestive of stone in the bladder when stones are not demonstrable on cystoscopic examination.

Diagnosis.—Often the diagnosis of diverticulum of the bladder may be made by cystoscopic examination, the mouth of the sac being observed on the bladder wall. Sometimes stones in the diverticulum may be seen protruding through into the cavity of the bladder, usually surrounded by an inflammatory area and granulation tissue. The cystoscopist can sometimes see where the nucleus of a stone, free in the bladder, has broken off from the stone projecting from a diverticulum. If the opening can be seen through the cystoscope a fair idea of its size and location is obtained by coiling a roentgenographic ureteral catheter in the sac and making a roentgenogram. In many cases, however, severe cystitis, obstructing prostate, or other cause prevents a satisfactory cystoscopic examination; in these cases a cystogram will usually give the data required.

Technic.—A roentgenogram is made of the vesical area; the bladder is then emptied completely with a soft rubber catheter, and the bladder filled comfortably full through the catheter with an emulsion of silver iodid, 2.5 to 5 per cent, or other nonirritating roentgenographic medium. The catheter is then removed and the patient tipped into a semi-Trendelenberg position. Several plates are made of the bladder at different angles, so that if a diverticulum is present the shadow will not be projected on the shadow of the full bladder in all the plates. The patient then voids, or if there is retention he is catheterized, and another roentgenogram is made which should show the outline of the diverticulum, the amount of retention in it, and whether or not shadows suspicious of stone are included in the diverticulum. With this technic a positive diagnosis can be made in almost every case. If there is a question of whether the shadows are in the ureter or in the diverticulum, the ureters can, of course, be excluded by means of lead catheters or a ureterogram.

Treatment.—The removal of a stone from the bladder when a diverticulum is present, or of a stone from a diverticulum, is not sufficient, since, if the original source of the stone remains, a recurrence is

to be expected. The diverticulum may be removed at the same time the stone is removed, or as a secondary procedure. The same pre-operative preparation should be employed as for prostatectomy, namely, removing the retained urine, clearing up infection, and building up the general health. In cases of large, foul diverticula it is often necessary to obtain drainage by suprapubic cystostomy and by tubes fastened into the diverticulum and into the bladder. A suprapubic excision of the sac and suture of the wall of the bladder are usually indicated. Whether this can be accomplished from the bladder side by invaginating the diverticulum into the bladder after the manner of Young, or whether the sac must be dissected free from the outside and the pocket it occupied drained, depends largely on the amount of infection and adhesions. Judd has pointed out that care must be taken in dissecting in order to avoid the ureter and vas which are often involved in the adhesions. It may be necessary to transplant the ureter into another portion of the bladder. The extravescical dissection is facilitated by a finger in the diverticulum (Judd), by distending the diverticulum with gauze (Lower), or by a rubber bag (Lerche). In the occasional case in which the diverticulum is shallow and the orifice small sufficient drainage can be obtained by enlarging the opening by a plastic operation or by fulguration through a cystoscope. The bladder in most cases is thick walled, with foul or even gangrenous cystitis.

MAYO CLINIC SERIES

The cases in this series are divided into three groups: Group 1, stone in the bladder without stone in the diverticulum, thirteen cases; Group 2, stone in both the diverticulum and the bladder, nine cases; and Group 3, stone in the diverticulum alone, six cases. The total is twenty-eight, 12.1 per cent of the 222 cases of diverticula.

Twenty-seven of the twenty-eight patients were males. The one woman in the series had a diverticulum of the base of the bladder, which was probably the result of an operation for the closure of a vesicovaginal fistula.

In fifteen cases the stones in the bladder were single, in seven they were multiple; twenty was the greatest number reported in any one case. The stones were reported to be large in nine cases. Stones in the diverticulum were single in eleven cases and multiple in four; with two exceptions they were of medium size.

In three cases the stone was wedged into the diverticulum with a portion projecting into the bladder; in two of these stones had previously been removed from the bladder in the Mayo Clinic. Small



FIG. 101 (Case A320659).—Lead catheter coiled in diverticulum. Diverticulum and bladder partially filled.



FIG. 102 (Case A320659).—Diverticulum and bladder completely filled. Cystogram.

diverticula of the base of the bladder had been noted, but they did not contain stones and were not removed. Both patients returned with a stone free in the bladder and a stone filling the diverticulum, with



FIG. 103 (Case A249315).—Lead catheters coiled in two diverticula of the bladder.



FIG. 104 (Case A249315).—Bladder and one diverticulum shown in cystogram.

a projection into the bladder through the small orifice. Through the cystoscope roughened areas could be seen on the stone in the bladder where they had broken off from the stone in the diverticulum. One of the stones was removed from the diverticulum suprapubically, the

diverticulum being excised at the same time. In the third patient the stone was not removed from the diverticulum. He was seventy-eight years old and in feeble health. He obtained symptomatic relief when



FIG. 105 (Case A344259).—One diverticulum filled and the bladder nearly empty.



FIG. 106 (Case A344259).—The diverticulum and the bladder filled.

the portion which projected into the bladder was removed with a specimen taken through the cystoscope. The fragment removed was pure calcium carbonate. This patient later returned with a third



FIG. 107 (Case A252495).—Roentgenograms of three stones in the bladder area.



FIG. 108 (Case A252495).—Two large diverticula filled, the bladder empty. The shadows of the stones are obliterated by the shadow of the diverticulum.

bladder stone, which was removed by litholapaxy. Two years elapsed between each recurrence. In a review of the literature only three cases of this type of dumb-bell stone filling a diverticulum and pro-

jecting into the bladder were found. One case was reported by **Davis**, one by **Young**, and one, observed in the Mayo Clinic, was reported by **Martin**. The two new cases included in this report make a **total of five cases**.

Benign prostatic hypertrophy was noted in eleven patients, stricture was noted in five, and atonic bladder in two. Residual urine was found in amounts varying from one-half ounce to complete retention in twelve patients. Twenty-seven patients had more severe cystitis than is uniformly found in uncomplicated cases of stone in the bladder.



FIG. 109 (Case A157750).—Roentgenogram of large dumb-bell stone filling a diverticulum and projecting into the bladder.

The walls of the bladders were often thickened and infiltrated throughout, and sometimes the mucosa was necrotic. Carcinoma was present in three patients; in one the malignant growth was near the mouth of the diverticulum, and apparently in one it had originated in the diverticulum. Two patients had a duplication of both ureters; this was the only congenital anomaly noted.

The smallest diverticulum was 2 cm. and the largest 9 cm. in diameter. Twenty-one patients had single diverticula; two had two each, and five had multiple diverticula. One diverticulum was multilocular.

The orifices of the diverticula were often recorded as "very small"; they opened into the base of the bladder in eleven; in the lateral walls in ten; in the posterior wall in two; and in the dome in two; the area was not recorded in six.

The inflammation in the diverticulum was often of greater severity than in the bladder itself.

That diverticulum is an etiologic factor in the formation of stone in the bladder is strongly suggested by the fact that of the twenty-eight patients three had passed many stones before coming to the Clinic; six had had stones removed at previous operations, one having had



FIG. 110 (Case A157750).—Stone shown in the roentgenogram in Figure 109, after removal from the bladder.

two operations. In the cases in which the diverticulum was not removed at the first operation in the Clinic there have been seven recurrences in four patients, five in the bladder, and two in the diverticulum. The total recurrences, therefore, were seventeen in thirteen patients. In cases in which the diverticulum was removed there were no recurrences of bladder stone. The high incidence of stone in these cases of 12.1 per cent is also suggestive of diverticula as etiologic factors.

Two patients with stone in the diverticula had had previous suprapubic cystostomy and the stones were not found. In one of these patients the stone was completely sealed over in the diverticulum with

inflammatory tissue and was diagnosed inoperable carcinoma; he had worn a suprapubic catheter for seven years and a large stone had formed in the bladder.

Treatment.—Of the twenty-one patients with stones in the bladder, suprapubic lithotomy was performed on seventeen, and litholapaxy on four; one died from a perinephritic abscess and sepsis without removal of the stone.

Eleven of the fifteen patients with stones in the diverticula underwent suprapubic operation; in one patient the stone was pushed into the bladder and litholapaxy performed; in one the stone in the bladder was removed and the patient died from carcinoma of the bladder; in one a suprapubic drainage only was done because of the extremely serious general condition of the patient complicated with gangrenous cystitis; in one operative procedures were not undertaken, the patient died from carcinoma of the larynx.

In one patient a combined bladder and diverticulum stone was removed suprapubically.

In seven cases the diverticula were excised; in one case two diverticula were excised. In six the diverticula were excised at the time the stone was removed, and in one at a later operation. In one case the diverticulum was opened into the prostatic urethra; in twenty the diverticula were not removed. (One diverticulum was removed elsewhere later.)

In five cases recurring bladder stones were removed by litholapaxy. In the two cases of recurring stone in the bladder and stone in the diverticulum the stone was removed from the diverticulum and the diverticulum obliterated suprapubically in one. In the other case the bladder stone was removed by litholapaxy; the stone was not removed from the diverticulum on account of the patient's age.

Mortality.—There were four deaths (14.2 per cent of twenty-eight). One patient died the seventy-second day after suprapubic removal of stones from the bladder and resection of a carcinoma at the mouth of the diverticulum. Death resulted from extension of the carcinoma. One patient died the seventeenth day after a suprapubic drainage for gangrenous cystitis; death was the result of renal insufficiency and sepsis. Two patients died without operation, one from carcinoma of the larynx, and one from perinephritic abscess and sepsis. There was no mortality following the removal of diverticula or of stones from diverticula.

CONCLUSIONS

Diverticula of the bladder occur more frequently than is usually supposed and may often contain stones.

The incidence of primary and recurring stone in the bladder seems higher than when there are no diverticula.

Diverticula are often overlooked both on examination and at operation. They may be easily diagnosed by means of the cystogram.

We should not be satisfied to remove a stone from the bladder, but should if possible correct the cause of its formation and thus prevent recurrence.

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SUBMUCOUS ULCER OF THE BLADDER IN THE MALE *

HERMON C. BUMPUS

Operations have been performed in the Mayo Clinic since December 1, 1916, in fifteen cases of submucous ulcer of the bladder. Two of these cases occurred in the male. In Hunner's initial article on this subject he used the title "Rare form of bladder ulcer" and contrasted the condition with the simple ulcer described by Fenwick. Since then several descriptive terms have been suggested for the infection; Cullen offered "Elusive ulcer" because of its difficulty of diagnosis. Geraghty proposed "Paracystitis" and more recently Keene proposed the comprehensive and inclusive term of "Pan-mural ulcerative cystitis." The term "submucous ulcer" is one that has been in use in the Mayo Clinic since the condition was first recognized.

Because the disease only slightly involves the mucosa and greatly involves the submucosal structure, the term seems to be concise and descriptive and to differentiate clearly the condition found from that of simple ulcers of the bladder in which the destruction is largely of the mucosa.

Although the etiology of the disease has remained in obscurity, there is nothing concerning it to indicate that it is confined to the female. Diseases of the female pelvic organs and pregnancy are apparently in no way associated with its onset. Since the practice of the physician who originally described the condition was confined to women he had not, obviously, observed cases in the male. He stated, however, that he believed the condition would be found in the male. A careful search of the literature, however, fails to reveal any reported cases in the male.

Focal infection has often been suggested as a cause of the condition, but from the clinical side alone proof of this has not been possible. The fact that the disease occurs in young adults (the average age in our

* Reprinted from the *Journal of Urology*, 1921, v, 249-253.

series was thirty-two at the time of onset) has been considered suggestive.

The condition indicates a blood-borne infection. The blood vessels are prominent, and as brought out by Keene, polymorphonuclear leukocytes are seen not only within the lumen, but infiltrating the vessel walls and paravesical tissues. There is also a marked diffuse submucous lymphocytic infiltration which together with the extravasation of the red blood cells through the surrounding tissue is added evidence of the infective origin of the lesion. The perivascular changes, cellular infiltration, and edema are usually most marked in the outer coats of the bladder. The mucosa frequently shows but slight involvement; the infection evidently is not carried by the urine since the tissues in contact with it are the least involved.

Eight of the fifteen patients showed periapical infection in their dental roentgenograms. Often many teeth were abscessed, a fact that led to experimental studies which resulted in demonstrating that from such areas of dental infection bacteria are obtainable. These bacteria, injected into laboratory animals, show elective affinity for the bladder and produce similar lesions in the bladders of the animals. The fact that the condition has been reported more frequently in the female remains unexplained. The two male cases here reported demonstrate that in this sex at least Cullen's term of "elusive ulcer" is still applicable.

The fact that an extensive pathologic process may occur in the bladder without producing changes in the urine, which are suggestive of the disease, has probably been a most potent factor in preventing the early diagnosis of the condition.

In both cases here reported the microscopic examination of the urine was negative as it was in eight others of the series. Yet both patients gave a history of intermittent attacks of gross hematuria in the past, as did the other thirteen of the series. Such hematuria has been noted by various observers and is explained by the ease with which the ulcer area can be made to bleed either by overdistention or by trauma; a condition frequently noted during cystoscopic examination and undoubtedly occurring when external pressure or long retention have occurred, which have produced the gross hematuria noted.

Such findings associated with a history of pain and frequency of equal severity by day and by night are pathognomonic of the disease; both of the male patients gave such a history.

In all of the cases in the series the first bladder symptoms dated

back eight years, the average was ten years. This illustrates quite as graphically as the numerous operations to which such patients are needlessly subjected how infrequently the disease is recognized.

We have records of eight of ten patients operated on more than one year. Four report complete cures, the other four no improvement. It has frequently been noted that when resection does result in cure it brings immediate relief. If this does not occur, inquiries bring the statement that the condition is unchanged; to be worse than before operation seems impossible. We believe that the high percentage of poor results may be due to the recurrence of the condition because of remaining foci. We are attempting to have such patients return and to have all foci removed, although it cannot be stated that the removal of the foci alone will always result in cure. We have two patients under observation who are opposed to surgery and are awaiting the results of eradication of foci. The bacteria from the teeth of both patients showed local affinity for the bladder when injected into laboratory animals.

REPORTS OF TWO CASES OCCURRING IN THE MALE

Case A18196. Mr. J. N., aged twenty-five years, first registered at the Clinic December 18, 1908. He complained of having had occasional cramps in the right abdomen for four years, lasting from ten to fifteen minutes, with marked soreness in the right lower quadrant during the past month. He had noticed some frequency and slight dysuria.

Cystoscopic examination and roentgenograms of the urinary tract were negative: the specific gravity of the urine was 1.015, the reaction was acid; there was a faint trace of albumin, no sugar, and a few hyaline and granular casts.

December 28, 1908, an acute perinephritic abscess was drained and a chronic appendix removed.

The patient returned to the Clinic eight years later, 1916, stating that his bladder condition had never improved and that he still had a day frequency of from six to eight and a night frequency of three or four, associated with sharp pain in the bladder when it was distended. Occasionally he felt burning, but he had never seen blood or gravel. With the bladder full he experienced slight incontinence.

The physical examination was negative except for slight suprapubic tenderness. The urinalysis, urine culture, roentgenograms of the urinary tract, and cystoscopic examination were negative. The patient was dismissed.

Three years later the patient returned again complaining as before, but with symptoms more severe; frequency was increased and incontinence with a full bladder was so much increased that he often wet his bed. His health otherwise was good.

Urinalyses and roentgenograms still remained negative, but cystoscopic examination revealed an area of increased reddening and edema in the posterior wall of the bladder near the dome; the vessels radiating from it were engorged. The remainder of the bladder was negative. The clinical symptoms and the cystoscopic findings all corresponded to the type of ulcer described by Hunner in the female. The diagnosis of submucous ulcer

of the bladder was made, and after the usual attempts at treatment by lavage, and so forth, the edematous area was resected March 28, 1919. The pathologist reported "Very marked submucous lymphocytic infiltration, extravasation of blood, epithelium markedly thinned (Hunner ulcer)."

Case A319426. Mr. F. H., aged thirty years, registered in the Clinic May 6, 1920. He complained of dysuria and stated that eight years before he had been sick for three months with ulcers of the bladder. He had had at that time marked frequency and hematuria. He apparently completely recovered and had no further symptoms until the onset of the present trouble five years before. He had sharp and very severe pain in the urethra lasting about half an hour, and was relieved by voiding. For the first few years this pain occurred at long intervals, but for the last three months it occurred every day and was associated with a day frequency of twelve and a night frequency of four or five. He also had a deep perineal pain, most extreme just before voiding. This disappeared immediately on urination.

The urinalysis showed a specific gravity of 1.010, acid reaction, slight trace of albumin, no sugar, and an occasional red blood cell. Roentgenograms of the urinary tract were negative. Cystoscopic examination showed an irregular, edematous area about 2 cm. in diameter in the dome of the bladder. This corresponded in appearance to the ulcers described by Hunner. Specimens of urine from both kidneys were negative. A diagnosis of submucous ulcer was made.

June 3, the bladder was opened. In the dome in the left side was found the area described. The bladder wall at this point was definitely thickened and seemed to be edematous. The mucous membrane was reddened and the peritoneum attached so that it was necessary to dissect it and resuture. An area about 4 cm. was excised. The pathologist reported an ulcer, 3 mm. in diameter, surrounded by a marked subepithelial inflammation.

SUBMUCOUS ULCERS OF THE BLADDER

	Cases.	Age at onset.	Sex.	Pregnancies.	Tonsillitis.	Grippe.	Rheumatism.	Abscessed teeth.	Duration of disease, years.	Gross hematuria.	Red blood cells.	Occasional pus cells.	Date of operation.	Cured.
1	169286	33	F.	0	+	-	-	-	3	+	+	0	12-6-1916	+
2	221983	36	F.	0	+	-	+	+	8	+	0	0	3-2-1918	0
3	224017	26	F.	2	+	-	-	+	30	-	-	-	3-25-1918	+
4	222836	31	F.	1	-	-	-	+	8	+	+	+	4-20-1918	-
5	245776	27	F.	1	-	+	+	-	9	-	0	+	10-9-1918	0
6	247841	45	F.	0	-	-	-	-	6	+	+	+	10-17-1918	0
7	255187	44	F.	2	-	-	-	0	5	+	0	0	1-21-1919	0
8	255050	39	F.	2	-	+	-	+	8	+	0	0	1-21-1919	+
9	18196	25	M.	-	-	+	-	+	11	+	0	0	3-28-1919	-
10	299174	24	F.	2	-	-	-	+	7	+	0	0	3-22-1920	+
11	314026	22	M.	-	-	-	-	-	8	+	0	0	6-3-1920	-
12	23637	33	F.	1	+	-	-	+	21	+	0	0	10-8-1920	-
13	340270	50	F.	1	+	+	-	-	8	+	0	+	12-21-1920	-
14	52145	26	F.	3	+	-	-	+	9	+	0	0	1-24-1921	-
15	348633	28	F.	1	+	+	-	0	8	+	+	+	2-15-1921	-

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SUBMUCOUS ULCER OF THE BLADDER AND ITS SURGICAL TREATMENT*

VERNE C. HUNT

Most types of ulcers of the bladder until recently have been treated by means other than surgical. The advent of cystoscopy has placed many of these lesions on a definite etiologic basis, and has shown that most of them are infectious in origin, usually secondary to infection elsewhere in the urinary tract. Ulceration of the bladder of renal origin may vary from the slightest inflammatory change in the mucosa of the bladder to an ulcerative cystitis of the entire bladder. The common ulcerative cystitis is usually easily recognized and ordinarily can be placed on a definite etiologic basis.

The so-called irritable bladder, that in the past has appeared to be negative on examination of the genito-urinary tract, has baffled urologists, and not until Hunner's first report (1914) of eight cases of "A rare type of bladder ulcer" was a definite pathologic basis presented to account for the symptoms in some cases. In subsequent papers Hunner has reported a total of twenty-five such cases. Since Hunner's first report approximately sixty-two similar cases have been reported in the literature: Hunner, twenty-five; Reed, five; Keene, ten (one of these cases was included in Hunner's series); Fowler, three; Kretschmer, five, and Bumpus, fifteen. The diagnosis was corroborated by operation in fifty-three cases.

Various terms have been used to designate the lesion; on the basis of its pathology we have chosen to call it submucous ulcer. It probably occurs more often than the number of reported cases would indicate.

Thirty-seven cases fulfilling all the requirements for the diagnosis of submucous ulcer of the bladder have been observed in the Mayo Clinic. In twenty cases operation was performed, and the diagnosis was corroborated. Bumpus reported fifteen of these. This report is also confined to the cases in which operation was performed.

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ETIOLOGY

The etiology of the lesion has been obscure since its first recognition. Many possible causes have been suggested, but until recently none has been supported by evidence of proof. The low incidence in the male suggests some cause peculiar to the female. Most observers agree, however, that pregnancy, pelvic infections, pelvic operations, and so forth, are not etiologic factors. Apparently they were not in our cases. Of the eighteen women in our series, thirteen had had one or more pregnancies; four had never been pregnant. Two had had symptoms immediately following confinement, and one during pregnancy. Three of the women were single and presented no evidence of genito-urinary or pelvic infection. Frequency and bladder irritability at times follow pelvic operations, but while many of our patients had been operated on previously, only one patient dated the symptoms from a pelvic operation, suspension of the uterus. Because of the location of the lesion in the dome or lateral walls of the bladder and the absence of infection in the urinary tract most observers agree that it is not a urine-borne infection. Hunner has suggested the teeth, tonsils, and sinuses as possible foci of infection; others have also suggested remote foci, and the accumulating evidence supports the theory of a blood-borne infection, placing the lesion on an etiologic basis with duodenal and gastric ulcers.

Rosenow's work on the selective affinity of organisms obtained from foci of infection suggested to Bumpus and Meisser a series of experiments which tend to show the selective affinity of certain strains of streptococci for the urinary bladder. Since in simple ulcers of the bladder and cystitis of unknown cause the urine contains the colon bacillus, this organism generally has been considered responsible. Bumpus and Meisser have shown, however, that pyelonephritis is often due to foci of infection harboring streptococci which have selective affinity for the urinary tract, and that the colon bacillus is of secondary importance. They report the results of the injection of thirty-three animals with cultures obtained from six patients with submucous ulcer of the bladder. Sixteen of nineteen animals injected intravenously with primary cultures from the teeth or tonsils had lesions of the urinary tract; thirteen of these were in the urinary bladder. On second animal passage, injection of streptococci, obtained from the lesions in the kidney and the urine of rabbits injected with the primary culture, produced lesions in the kidney in four of the five animals. In nine animals injected with

cultures from the urine of the patients, lesions of the urinary tract occurred in six of seven in which the culture contained streptococci, and in neither of the two in which the culture contained only the colon bacillus. Bumpus and Meisser furthermore demonstrated diplococci within the submucous ulcer excised in two patients. The results of their investigation, it seems, justify their conclusion that submucous ulcer and other infections of the urinary bladder may be due to focal infections harboring streptococci which have a selective affinity for the urinary tract.

Since the teeth, tonsils, and sinuses are foci of infection common to the male and female, some additional etiologic factor other than focal infection must explain the frequency of the lesion in the female and its rarity in the male.

PATHOLOGY

The detailed pathology of submucous ulcer has been described by Hunner, Kretschmer, and others, and their agreement in the essentials of its pathology is assurance that the lesions in the cases reported are all of the type first described by Hunner. Suffice it to repeat that the ulcer develops as the result of chronic inflammation involving all coats of the bladder; it usually is surrounded by a varying amount of edema which may involve the major portion of the bladder dome and at times extend into the paravesical tissues. This, as the results of surgical treatment show, is of great importance in the surgical treatment of the lesion.

The ulcer is usually single, but may be multiple. It was single in most of the reported cases, and in only one of our surgical cases were there two ulcers. The lesion is found in the free portion of the bladder. In our series it occurred in the dome in thirteen cases, in the posterior wall in three, in the left wall in two, and in the right wall in two. The ulcer itself is usually small. In our series it varied in diameter from 3 mm. to 2.5 cm.; in fourteen cases it was 1 cm. or more in diameter. While the true ulceration is small the edema and inflammatory reaction about the ulcer may be very extensive.

SYMPTOMS

The symptoms have been described by the various observers; those in the reported cases and in our cases are quite uniform: pain, frequency, and bladder irritability are present in all. The pain is not always con-

fined to the bladder, but at times is referred to the perineum and rectum and often to the inguinal region on the same side as the ulcer. The irritability necessitates voiding every few minutes and is little alleviated by change in the reaction of the urine or by lavage of the bladder.

The lesion occurs most frequently in the middle decade of life. Our youngest patient, at the time of admission to the Clinic, was twenty-eight years of age, and the oldest fifty-six, an average of forty and seven-tenths years. The average duration of symptoms before admission to the Clinic was eight and seven-tenths years. The youngest age at the time of onset was nineteen years, the oldest forty-nine; the average was thirty-two. This average is somewhat higher than that in Hunner's series of twenty-five cases, in which it was twenty-five years. However, the average duration in his cases was thirteen years and the average age of the patients at the time of consultation thirty-eight years. The slight variations in these ages is of little consequence; the figures are important, however, since they show that the symptoms of this particular lesion are persistent for years, and that the lesion has been particularly resistant to all forms of treatment to which it has been subjected.

DIAGNOSIS

The diagnosis of submucous ulcer of the bladder is based on the history, urinalysis, and cystoscopic findings. Hunner states: "Given a patient who has had years of bladder misery in spite of many courses of treatment, who has clear urine macroscopically, free from infection, but containing blood cells and leukocytes, and cystoscopic examination reveals one or more ulcers, one is justified in making a diagnosis of this type of ulcer."

In our cases pain and frequency were the predominating symptoms, and they were present in all cases; tenesmus was associated in nine cases. Fourteen of the patients gave a history of hematuria, while examination of centrifuged urine showed no red blood cells in eleven cases, but small numbers in nine. The examination of centrifuged urine in seven cases was entirely negative for microscopic elements. Pus cells were found in thirteen cases, but in none of these were they present in more than small numbers. Cystoscopic examination did not disclose evidence of cystitis or infection of the urinary tract, except the localized area of edema or inflammatory reaction about the ulcer.

TREATMENT

Patients with submucous ulcer of the bladder have been subjected, by virtue of the long duration of symptoms, to all types of treatment, including lavage of the bladder with various solutions, suprapubic drainage of the bladder, and fulguration of the lesion. Little more than slight or temporary amelioration has been accomplished in most instances. Previous to the recognition of the true cause of symptoms many patients were subjected to pelvic and abdominal operations without success. The cause of "irritable bladder" was not attacked directly by surgical methods until its recognition by Hunner. On the pathologic basis of this type of ulcer, that is, a chronic inflammatory process involving all coats of the bladder and usually surrounded by a varying area of edema, Hunner advocates wide excision of the ulcer and the edematous bladder wall. He attributes recurrence after resection to incomplete removal of the edematous bladder wall.

RESULTS OF SURGICAL TREATMENT

In view of the suggested etiology of submucous ulcer of the bladder and a review of our cases in an effort to ascertain the results of surgical excision of the ulcer, it seems that surgical treatment of the lesion is often insufficient for the complete eradication of the ulcer and the elimination of the possibility of recurrence.

The immediate results following wide excision of the entire thickness of the bladder wall and the surrounding inflammatory tissue were excellent in our series; practically all the patients were free from their symptoms or were markedly improved on leaving the hospital and on dismissal from the Clinic. The ultimate results, however, have not been so good. Seventeen of the twenty patients operated on have reported to us. Five are well and entirely free from bladder symptoms, two after three years since operation, one after two and one-half years, one after two years, and one after one year. Five patients report improvement since operation, one after three years, one after two years, one after nine months, and two after four months. Three patients report no improvement following operation; two after three years, and one after six months. Four patients experienced temporary complete relief, with subsequent recurrence of all symptoms, one patient after two years, two after one year, and one after six months. Cysto-

scopic examination of one of these patients after one year of relief disclosed a recurrence of the ulcer.

In all of the cases, except those of Keene, reported in the literature, that have been treated by surgical measures, the immediate and not the late results have been stated. Five of the eight cases which Hunner first reported were treated by surgical excision of the ulcer. Not more than eight months had elapsed since operation in any case except that of his first patient, who had remained well for six years. The results in his Case 3 were good after two months, in Case 4 after six months, and in Case 8 after eight months. A recurrence of the symptoms took place in Case 5 two months after operation, which the author attributes to incomplete removal of all the edematous tissue about the ulcer. In a subsequent paper Hunner reports a recurrence of symptoms in Case 3 one and one-half years after operation, and evidence of recurrence of the ulcer on cystoscopic examination, recurrence of symptoms in Case 9 one year after operation, and in Case 12 one and one-half years after operation.

The time elapsing since operation in Keene's cases ranges from two months to two and one-half years, with recurrence in Case 2 after seven months. The period since operation was two and one-half years in Case 1, two years in Case 2, twenty-three months in Case 3, twenty-one months in Case 4, sixteen months in Case 5, nine months in Case 6, three months in Case 7, and two months in Case 8.

Kretschmer's cases were all reported within six months of the operation, too short a time to ascertain the ultimate results. The same is true of Reed's three surgical cases.

It is obvious from the review of this series that the ultimate results of the surgical treatment of submucous ulcer cannot be accurately stated immediately after operation, for, while most recurrences result within a year, it seems that the possibility of recurrence cannot be eliminated within two years after operation. Even though permanent good results by surgical methods cannot be assured in all cases of submucous ulcer, the large number of cases in which complete relief, and those in which temporary relief or benefit is obtained from operation, make the surgical excision of this type of ulcer warranted in all cases. Hunner states, "No type of treatment suffices except wide excision of the inflammatory area." To this demand, in the light of the advances which have recently been made in establishing the cause of the lesion, should be added the elimination or removal of all foci of infection, par-

ticularly in the teeth, tonsils, and sinuses. The removal of such foci in conjunction with wide surgical removal of the ulcer should increase the percentage of permanent relief and decrease the number of recurrences.

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ROENTGEN RAY AND RADIUM IN THE DIAGNOSIS AND TREATMENT OF CARCINOMA OF THE PROSTATE*

HERMON C. BUMPUS, JR.

The favorable results reported by Pasteau and Degrais (1910) in the treatment of cancer of the prostate by radium inspired the hope that a satisfactory treatment for this condition had been discovered. Since then many others have reported similar results, but such reports have been made too soon after treatment, or the series of cases reported has been too small on which to base judgment. Neither have there been series of cases reported of what might be termed normal or untreated cases with which to compare results. Thus it has been difficult to judge accurately the results obtained with the use of radium.

The series of 646 cases of carcinoma of the prostate which I shall report is sufficiently large to afford statistical data of value with regard to the various forms of treatment employed, especially radium. Until within recent years correct diagnoses in cases of cancer of the prostate were often not made unless the patients were operated on. Thus many cases were classified as benign hypertrophy which were undoubtedly malignant.

During the past three years 1641 patients with prostatic enlargement were examined. In 260 of these (15.84 per cent) the prostates were malignant, a percentage which I believe is accurate and indicative of the prevalence of the disease. In the series of 646 patients the prostate was removed in 146, no form of treatment was employed in 325; the remaining 197 patients were treated by radium. The statistics in the first two groups afford a basis on which the results of radium treatment in the 197 patients may be compared.

The results of surgical treatment are tabulated in Table 1.

* Reprinted from the American Journal of Roentgenology, 1922.

TABLE 1
ONE HUNDRED FORTY-SIX PATIENTS OPERATED ON
(Operative Mortality 5.5 per cent)

	Patients.	Per cent.	Average duration of disease, months.	Prostatectomy.*		Average length of life after operation, months.	Average age, years.
				Perineal.	Suprapubic.		
Heard from.....	120		62.36	42	75	24.86	64.27
Dead.....	96	80.0	51.3	41	52	21.72	64.95
Living.....	24	20.0	80.2	1	23	35.2	63.58
Patients who lived							
1-12 months.....	41	34.16	40.4	19	22	6.18	65.8
13-24 months.....	23	19.16	45.95	8	15	18.86	63.13
25-36 months.....	14	11.66	56.64	8	6	38.14	65.07
37-48 months.....	1	0.83	168.0	1	0	41.0	62.0
49-60 months.....	3	2.5	77.33	1	2	53.3	65.0
61-72 months.....	2	1.66	95.5	1	1	70.0	60.5
83-96 months.....	1	0.83	168.0	1	0	96.0	64.0
97-108 months.....	2	1.66	156.0	0	2	103.5	72.0
Not stated.....	9	7.5		2	4		
Patients living							
1-12 months.....	4	3.33	66.75	0	4	10.2	64.75
13-24 months.....	8	6.66	67.85	0	8	19.87	66.25
25-36 months.....	5	4.16	71.0	0	5	31.8	61.4
37-48 months.....	1	0.83	87.0	0	1	48.0	69.0
49-60 months.....	2	1.66	83.0	0	2	52.5	53.5
61-72 months.....	2	1.66	83.0	0	2	67.5	59.0
73-84 months.....	1	0.83	139.0	0	1	78.0	75.0
109-120 months.....	1	0.83	174.0	1	0	120.0	61.0

* Operation not stated in three cases.

DISCUSSION OF TABLE 1

The fact that 80 per cent of the patients died within two years after operation and that of the sixteen patients who lived more than three years only seven are alive explains the readiness with which surgeons relinquished this group of cases to radium treatment.

Just as in the past reports of the results of surgical treatment were made too soon after operation to be accurate, so in the present the reports of the results of radium treatment are made too soon to afford accurate data. It is evident that in order to judge accurately the various forms of radium treatment it is fairer to compare data from a series of patients who have not been treated than from a series of patients treated surgically who were in good physical condition and in whom the disease was not far advanced.

The group of 325 untreated patients includes patients in all stages of the disease and represents the types that have been treated with radium. Information has been received concerning 231 of these (71 per cent), thus affording an opportunity to study the disease when its course was not altered by treatment and to compile accurate statistics as a basis of comparison with the results of several methods of radium treatment.

TABLE 2
THREE HUNDRED TWENTY-FIVE PATIENTS NOT TREATED

	Patients.	Per cent.	Average duration of disease, months.	With metastasis.	Without metastasis.	Average length of life after examination, months.	Average age.
Heard from.....	231		34.59	55	176	11.8	64
Dead.....	215	93.0	32.82	52	163	9.58	64
Living.....	16	6.9	59.15	3	13	39.06	66
Patients who lived							
1-12 months.....	149	64.5	29.1	42	107	4.97	64
13-24 months.....	32	13.85	41.66	9	23	17.53	65
25-36 months.....	8	3.46	46.28	0	8	28.37	67
37-48 months.....	3	1.29	75.0	0	3	44.3	67
49-60 months.....	2	0.86	68.0	0	2	52.0	68
73-84 months.....	1	0.43		0	1	78.0	69
Not stated.....	20	8.65		1	19		
Patients living							
1-12 months.....	4	1.73	10.0	1	3	19.3	66
13-24 months.....	4	1.73	32.7	2	2	19.75	68
25-36 months.....	1	0.43	149.0	0	1	29.0	70
37-48 months.....	2	0.86	120.0	0	2	47.0	68
49-60 months.....	1	0.43	49.0	0	1	49.0	66
61-72 months.....	2	0.86	73.0	0	2	70.0	63
73-84 months.....	1	0.43		0	1	79.0	63
108-120 months.....	1	0.43	144.0	0	1	118.0	62

DISCUSSION OF TABLE 2

The noteworthy fact in this series is that the patients who died, in whom, therefore, the disease had run its course, lived an average of 9.58 months after they were examined and an average of 32.82 months from the time of their first symptoms; this may be considered representative of the average duration of the disease. The sixteen patients (6.9 per cent) who are still alive constitute two types, those who recently refused treatment and who have not lived out their full term, 32.82 months, and those whose cases were wrongly diagnosed.

percentage seems remarkably low when it is considered that the diagnoses were all made by palpation alone and were not checked up by pathologic findings as were the diagnoses in the surgical group. The low percentage is undoubtedly due to the fact that when the diagnosis was in doubt the patient was given the benefit and operation was performed. It does not seem legitimate, however, to use these percentages as a basis of comparison in ascertaining the results of radium treatment, since fifty-five of the patients had metastasis at the time of their examination.

While opinions differ concerning whether or not radium and roentgen-ray treatments are beneficial in cases in which metastasis has occurred, I believe that all observers are agreed with regard to the influence of metastasis on prognosis.

TABLE 3
NINETY PATIENTS WITH METASTASIS

	Patient.	Per cent.	Average duration of disease, months.	Average length of life after examination, months.	Average age, years.
Heard from.....	55		28.78	8.15	63.4
Dead.....	52	94.54	29.25	7.72	63.5
Living.....	3	5.45	21.3	15.0	64.0
Patients who lived					
1-12 months.....	42	76.36	27.51	5.56	62.42
13-24 months.....	9	16.36	37.75	17.1	67.6
Not stated.....	1	1.81			
Patients living					
1-12 months.....	1	1.81	10.0	8.0	65.0
13-14 months.....	2	3.63	27.0	18.5	63.5

DISCUSSION OF TABLE 3

The influence of metastasis on prognosis is illustrated in the group of fifty-five patients, 94.54 per cent of whom died on an average of 7.72 months after their examinations, two months earlier than the average. It is probable that the majority of patients with carcinoma of the prostate develop metastasis some time before death, but in some this occurs early and the presence of many such patients in this group explains the shortening of the average duration of the disease, which was 29.25 months, four months less than the average.

It may also be noted that the average age of these patients years, is below the general average of the patients with the disease.

The fact that 76.36 per cent of these patients died during the ensuing years is sufficient evidence of the hopelessness of the condition. Palliative treatment, such as roentgen ray or radium, was therefore attempted in these cases. The smallness of this group, consisting of 27.6 per cent of the patients examined, is evidence that until now years it has not been appreciated how frequently metastasis occurs, especially in the bones.

TABLE 4
METASTASIS REVEALED BY ROENTGENOGRAMS: 228 PATIENTS

	Examined.	Metastasis.	Per cent.	Age
Total.....	228	69	30.26	63.
Pelvis.....	153	46	30.7	62.
Spine.....	154	40	25.97	62.
Lungs.....	140	8	6.4	65.
Ribs.....	141	8	5.0	66.
Femurs.....	122	7	5.7	63.

DISCUSSION OF TABLE 4

Of the 646 patients, only 228 (35.29 per cent) were examined roentgenographically for metastasis, and of this number, 163 (71 per cent) were examined during the past three years. In the early case the roentgen ray was not as easily available as it is now, and the impression seemed to prevail that it was sufficient if the chest was examined for metastasis. This accounts for the fact that until within the last few years more roentgenograms were made of the chest than of the spine or pelvis. Data compiled previous to the last year showed that the chest was involved in 37.5 per cent of cases, the lumbar spine in 35.8 per cent, and the lungs in 3 per cent; the latter were never involved unless metastasis was demonstrable elsewhere. It is significant that these percentages, which were compiled from a series of only 135 cases, still hold true in this larger series of 228 cases in which the pelvic bones were involved in 30 per cent, the spine in 25.97 per cent, and the lungs only 6 per cent.

The data in Table 4 shows that if the spine, the pelvis, and the femurs are examined by the roentgen ray routinely in all cases of advanced prostates suspected of being malignant, a negligible number of cases of metastasis will remain undiscovered. It does not seem

sary to examine the chest as a routine procedure since metastasis to the lungs alone probably never occurs in these cases. It would seem conservative to state that 30.26 per cent or practically one-third of all patients with carcinoma of the prostate will be found to have metastasis to the bones, and in the overwhelming percentage it will be found in the pelvis, the spine, and the femurs. The average ages of the patients also bear evidence of the lateness of metastasis to the lungs. The average age in the entire series of 646 patients is 64.6 years, the average age of patients with metastasis to the pelvis and spine is from one to two years



FIG. 111 (Case A181438).—Extensive metastasis of the sacrum, lumbar spine, and ilia.

less, and of patients with metastasis to the lungs and ribs from one to two years more, demonstrating still further that metastasis does not occur in the chest until after it occurs in the spine and pelvis.

Stewart believes that in the majority of cases of metastasis to the bones the primary growth can be diagnosed by the roentgenographic appearance of the metastasis. He quotes from Phemister as follows:

Metastasis in bony structure following a primary carcinoma assumes the characteristics of the original growth; if the stroma predominates in the primary lesion, we are sure to have a condensing or osteoplastic form of metastasis; if the primary cancer were of a medullary form, we would have a secondary rarifying or osteoclastic process.

Stewart calls attention to the fact that in carcinoma of the prostate the stroma predominates, and a condensing form of secondary metastasis should occur (Figs. 111 and 112). This is in keeping with von Reckhausen's findings and applies to the majority of cases, but as may be seen in Figure 113 osteoclastic metastasis also occurs, and although it occurs infrequently there is little chance of error in the diagnosis. The osteoplastic type of metastasis is found in the majority of cases.



FIG. 112 (Case A104448).—Area of metastasis in the right lung.

The close similarity of this type to Paget's disease has recently been emphasized by Carman and Carrick; this may be readily appreciated by examination of Figures 114 and 115, in which the two conditions in similar locations are illustrated for comparison.

In cases in which the prostatic enlargement is unquestionably malignant, the possibility of error in diagnosis is negligible. However, there is a less frequent form of prostatic malignancy in which the enlargement is uniform without any of the irregularities of carcinoma.

presented by the common type of carcinomatous gland and without the characteristic stony hard areas. This type of malignant gland resembles true inflammatory hypertrophy and often is confused with it, but it differs in that the resilience is lost, while in inflammatory disease it always remains. Such glands never reach a size that cannot be outlined by the examining finger, because they are composed of cells which exhibit no tendency to acinus formation, but are scattered throughout a somewhat increased fibrous stroma and metastasize so early that death results before the gland becomes greatly enlarged. A section



FIG. 113 (Case A289964).—Destruction of right ischium, as the result of a metastatic growth in which the osteoclastic tendency predominates.

from this type of gland (Fig. 116) illustrates its close resemblance to scirrhous carcinoma of the breast. The reason for early metastasis is shown by the cells infiltrating a somewhat increased fibrous stroma and exhibiting no tendency to acinus formation. In such cases the rheumatic pains of metastasis or the paraplegia of spinal involvement are frequently the first symptoms, and the patients often die before any urinary symptoms occur to call attention to the prostate as the primary focus of extensive metastasis to the bones. Or, if the prostate is examined, its slight enlargement and its atypical feel of carcinoma

make a diagnosis of malignancy doubtful. If it cannot be determined that the prostate is malignant, and there are no urinary symptoms, the condition may be Paget's disease. The mistake has been made of diagnosing as malignant an old firm inflammatory prostate because roentgenograms revealed what was supposed to be metastasis to



FIG. 114 (Case A345243).—Metastasis to the spine from carcinoma of the prostate.



FIG. 115 (Case A343042).—The spine in a case of Paget's disease. Greater flattening and deformity of the vertebræ are shown than in Figure 114.

bones. In Paget's disease the bodies of the lumbar vertebræ are flattened and widened, while in malignant conditions there is little if any change in the shape of the vertebræ. However, as Carman and Carrington point out, there is one means of making the diagnosis certain, "If the skull shows the pathognomonic changes of Paget's disease, that

thickening and density of the inner table and the finely porous outer table with scattered nodules of bone over the vault, the diagnosis of Paget's disease is certain." Therefore, in all cases of apparent metastasis to the bones in which the prostate is suspected of being malignant, roentgenograms should be made of the head before a positive diagnosis is made. From the foregoing it is evident that if the untreated cases are used as a basis of comparison of results obtained from radium

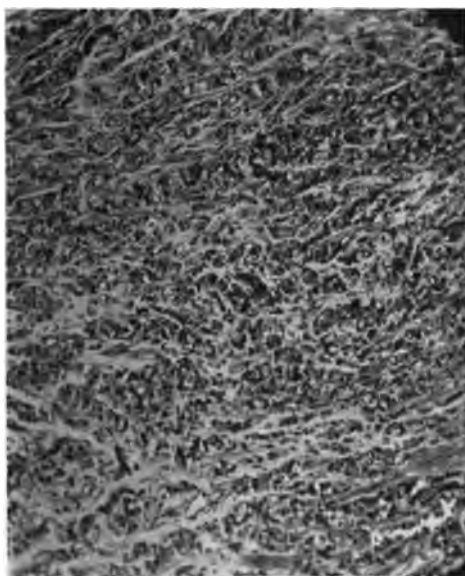


FIG. 116 (Case A20348).—Highly malignant adenocarcinoma ($\times 100$). This type causes only slight local enlargement, but metastasizes early, often resulting in the metastasis being confused with Paget's disease because of slight prostatic enlargement.

therapy, the cases in which metastasis was found must be excluded (Table 5).

DISCUSSION OF TABLE 5

Since the patients who received radium treatment were treated immediately following the diagnosis, it seems logical to consider the length of life of the untreated patients following the diagnosis to be comparable with the length of life of those who received treatment. This period in the untreated patients is 12.98 months, or thirteen months.

TABLE 5
TWO HUNDRED THIRTY-FIVE PATIENTS WITHOUT TREATMENT AND WITHOUT
METASTASIS

	Patients.	Per cent.	Average duration of disease, months.	Average length of life after ex- amination, months.	Average age, years.
Heard from.....	176		36.61	12.98	65.2
Dead.....	163	92.6	34.08	10.13	65.0
Living.....	13	7.3	70.5	44.61	67.2
Patients who lived					
1-12 months.....	107	60.79	29.72	4.76	65.1
13-24 months.....	23	13.1	43.09	17.69	64.2
25-36 months.....	8	4.5	46.28	26.37	67.5
37-48 months.....	3	1.7	75.0	44.3	67.0
49-60 months.....	2	1.13	68.0	52.0	68.5
73-84 months.....	1	0.56		78.0	69.0
Not stated.....	19	10.79			
Patients living					
1-12 months.....	3	1.7	10.0	9.66	67.0
13-24 months.....	2	1.13	38.5	21.0	74.0
25-36 months.....	1	0.56	149.0	29.0	70.0
37-48 months.....	2	1.13	120.0	47.0	68.5
49-60 months.....	1	0.56	49.0	49.0	66.0
61-72 months.....	2	1.13	73.0	70.0	63.5
73-84 months.....	1	0.56		79.0	63.0
108-120 months.....	1	0.56	144.0	118.0	62.0

In order not to base such an extensive statistical study on a short period of time the duration of the disease in each case from the first symptom to the time of death has been obtained. These data are subject to a certain degree of error, since carcinoma may develop on benign hypertrophy and the first symptoms may be due to the benign hypertrophy rather than to the malignancy. However, the group of patients with atypical carcinoma of the prostate who do not have symptoms until the disease is well advanced offsets this error and it seems accurate to consider the average length of the disease to be 36.61 months, three years, and the average duration of life after diagnosis, thirty-two months. These periods are used as the basis for judging the results of the various methods of radium application. Besides these averages there is recorded for comparison in each group the number of patients that died in each year after treatment, for it is evident that if averages alone are used as the basis of comparison, the few successfully treated patients become merged in the general average and their importance

as a basis of comparison is lost. Also, in considering the length of the disease, it must be kept in mind that the patient is never considered cured, and if the length of the disease has been extended by any method of treatment beyond the three-year average period for untreated cases, it is considered favorable.

TECHNIC OF RADIUM TREATMENT

In the first cases of carcinoma of the prostate treated by radium the radium was introduced through the urethra. In well advanced cases, however, the necessity of applying large doses resulted in urethral burns. Cross-firing was then attempted by applying half the dose through the rectum. The mucosa of the rectum proved to be even more susceptible to burns than that of the urethra and great care was necessary in screening and in regulating the duration of the exposure. An applicator similar to the one described by Young was used, the rectal mucosa being protected by brass and lead screens except at the point of exposure. The treatments were given every third or fourth day until the desired dosage was obtained. Forty patients, including seven in which both urethral and rectal applications were given, were treated in this manner. Information has been obtained concerning thirty-seven (92.5 per cent) of these (Table 6).

TABLE 6

FORTY PATIENTS TREATED BY RADIUM THROUGH THE RECTUM AND THE URETHRA

	Patients.	Per cent.	Average duration of disease, months.	Average duration of treatment, months.	Urethra.	Rectum.	Milligram hours.	Average length of life after radium treatment, months.	Average age, years.
Heard from.....	37		44.09	2.96	250.0	1537.91	1585.2	18.27	66.2
Dead.....	33	89.18	42.2	2.5	225.0	1581.9	1622.8	15.31	62.6
Living.....	4	10.81	62.3	1.2	400.0	1175.0	1275.25	42.0	70.75
Patients who lived									
1-12 months.....	17	45.94	33.4	1.23	220.0	1162.6	1296.1	6.64	63.58
13-24 months.....	7	18.91	39.0	2.68		1503.4	1503.4	17.0	66.0
25-36 months.....	6	16.21	57.5	5.55	250.0	2269.0	2310.6	26.6	69.6
37-48 months.....	2	5.4	93.0	4.7		3250.0	3250.0	43.0	67.5
Not stated.....	1	2.7							
Patients living									
37-48 months.....	4	10.81	62.3	1.2	400.0	1175.0	1275.25	42.0	70.75

DISCUSSION OF TABLE 6

The technic employed in the treatment of these forty patients has several distinct advantages, the most important of which is the great amount of radiation reaching the periphery of the growth in which location the greatest cell activity occurs. The application is easily accomplished and a comparatively small amount of radium is required, a standard tube of 50 or 100 mg. being sufficient. The applicator is of simple design and adapted to general use. The chief drawbacks were the irritability of the rectal mucosa which frequently did not permit the amount of radiation indicated even with the greatest care in screening. Although the area of greatest cell activity receives the greatest amount of radiation, yet even in moderately enlarged glands comparatively small amounts of radiation reach the center of the growth where cell activity, although not so active, nevertheless takes place. Therefore, unless all portions of the growth receive sufficient dosage to improve this activity, satisfactory results cannot be expected.

With these disadvantages in mind, it is interesting to observe the clinical results recorded in Table 6. In these the average length of disease was forty-four months, eight months longer than the average for untreated patients. The average length of life after treatment was eighteen months, five months longer than could be expected if no treatment had been given. While these data are evidence of an inhibitory influence of radium on the disease, this inhibitory influence is not sufficient to commend the treatment. For merely to delay the inevitable for a short period rather than appreciably to arrest the disease process is a result which is not to be sought when death is only more longed for than dreaded.

Statistics of the average length of life are valuable, but they must not be taken as final since they may obscure several cases in which the results indicate marked advantages to such treatment. For example, six patients (16.21 per cent) lived more than three years; four are still alive, while only seven (3 per cent) of those not treated are alive three years after examination. This is encouraging when the hopelessness of the condition is considered, but not encouraging enough to warrant urging the patient to take the treatment with considerable expense and inconvenience. Marion, realizing the difficulty of properly radiating all parts of the gland by this method, and probably being cognizant of the clinical results, inserted a trocar directly into the su-

stance of the gland, and by means of the obturator placed the radium tube directly into the tissue. The tube was withdrawn by means of an attached string after the required application.

Barringer described a similar but far superior method. He placed the radium in a hollow needle, and, guided by a finger in the rectum, inserted it directly into the gland through the perineum. This method seemed so superior to all others that the earlier procedures were for the time abandoned. The cases so treated are reported in Table 7.

TABLE 7
THIRTY-FIVE PATIENTS TREATED BY NEEDLES

	Patients.	Per cent.	Average duration of disease, months.	Average duration of treatment, months.	Needles.	Milligram hours.	Average length of life after radium treatment, months.	Average age, years.
Heard from.....	20		39.68	1.5	1201.9	1201.9	11.0	63.95
Dead.....	18	90.0	41.05	1.75	1250.94	1250.94	10.47	63.5
Living.....	2	10.0	28.0	1.0	760.0	760.0	15.0	68.0
Patients who lived								
1-12 months....	10	50.0	37.6	1.17	1246.1	1246.1	5.4	61.3
13-24 months....	7	35.0	29.6	2.76	1657.6	1657.6	17.0	65.4
Not stated.....	1	5.0						
Patients living								
1-12 months....	1	5.0	29.0	1 da.	850.0	850.0	7.0	68.0
13-24 months....	1	5.0	27.0	1 da.	671.0	671.0	24.0	68.0

DISCUSSION OF TABLE 7

The thirty-five patients whose cases are reported in Table 7 were treated by means of needles alone. The average length of the disease in the twenty patients heard from in this group is prolonged approximately four months beyond the normal three years. The average length of life, however, after such treatment is two months less than of those not treated. The dosage in this series averaged 1200 mg. hours, approximately 455 mg. hours less than in the group in Table 6. The decreased dosage is not a sufficient reason to explain the poorer results obtained, results which are still more strikingly brought out when the individual cases are examined. Ten (50 per cent) of the patients died the first year after treatment; seven of the remaining ten died the second year. The date of one patient's death is not given, and

the two living patients have not yet lived two years after treatment. Regrettable as these results may appear they are nevertheless valuable for they demonstrate clearly that neglect to radiate the periphery of growth, where the greatest cell activity occurs, will result in failure. They also show that if radium is placed within the gland tissue gamma rays do not penetrate sufficiently to reach the peripheral cancer, or, if they do, are too greatly diffused to be effective. It was evident

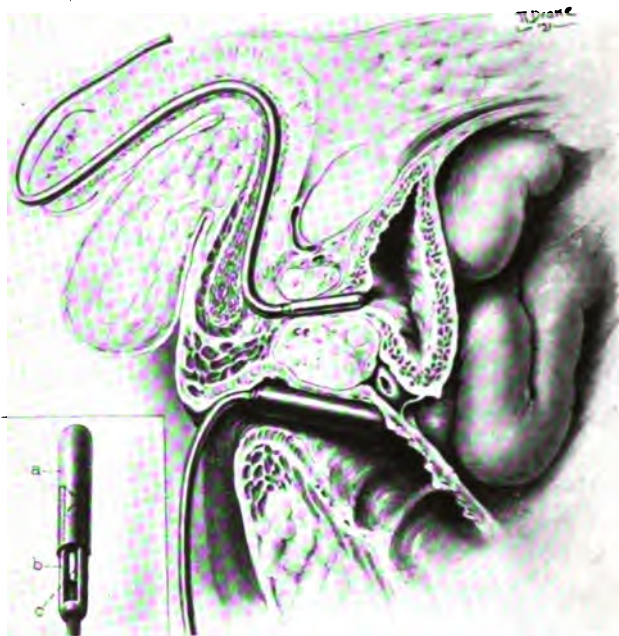


FIG. 117.—Cross-section through the pelvis. Rectal and urethral applicators in place. Insert, rectal applicator, (a) hard rubber sheath, (b) lead spoon, and (c) standard radium tube.

therefore, that the amount of radium should be increased, and an attempt was made to give, if possible, between 3,000 and 4,000 hours, 2,000 by needles, the remaining 1,000 by rectum and urethra.

In giving this larger dosage a modification of the old applicators were found useful. The great majority of such apparatus consists of an arm attached to the examining table which holds in place a metal tube containing the radium. It was found, however, that a piece of sheet lead cut in the shape of a spoon (Fig. 117) is the most satisfactory

applicator. The small metal container holding the radium is placed in the bowl and the lead is bent over three sides of it. Over this a hard rubber tube is slipped to filter the beta rays on the exposed side; thus the rectal mucosa is screened by lead except the portion directly over the prostatic area; there the irritating rays are filtered out by the hard rubber tube. When the applicator is inserted and placed in the desired position the open side of the bowl is placed next to the prostate, the handle is bent at right angles and attached to the thighs or buttocks by surgeon's plaster. This method allows the patient to move around freely while recumbent and while the applicator is still in position, instead of subjecting him to the discomfort of remaining in one position on an examining table to which a rigid mechanical arm is attached. In making the urethral applications, screened only by the standard silver container, nothing has proved so useful as a stick of soft solder, the end of which is threaded so that the container may be directly screwed on. The stick of solder can be bent to adapt it to the various prostatic curves, and is easily kept in position (Fig. 117).

The results of the increase in dosage and more thorough radiation of the prostate are difficult to interpret, because this group of patients was treated more recently than the others. A casual examination of Table 8 might lead to the conclusion that the change in treatment had not resulted in improvement.

TABLE 8

NINETY-SEVEN PATIENTS TREATED BY NEEDLES AND BY URETHRA AND RECTUM

	Patients.	Per cent.	Average duration of disease, months.	Average duration of treatment, months.	Needles.	Urethra.	Rectum.	Milligram hours.	Average length of life after radium treatment, months.	Average age, years.
Heard from.....	66		34.37	6.9	1655.9	304.95	437.47	2240.72	12.76	64.33
Dead.....	30	45.45	28.96	4.32	1144.7	352.88	425.55	1625.46	11.26	64.9
Living.....	36	54.54	39.88	7.56	2081.91	291.03	448.69	2753.44	13.91	63.86
Patients who lived										
1-12 months.....	19	28.78	26.52	2.37	1242.68	374.33	319.61	1609.15	6.94	65.57
13-24 months.....	8	19.12	32.42	6.4	777.5		402.5	1180.0	18.5	62.57
25-48 months.....	1	1.51		3.2	2002.0	550.0	2870.0	5492.0	38.0	55.0
Not stated.....	2	5.05								
Patients living										
1-12 months.....	19	28.78	40.94	4.6	1627.0	274.22	471.0	2410.42	8.94	64.21
13-24 months.....	15	22.72	38.07	8.49	2593.73	330.5	544.26	3255.73	17.89	63.6
25-36 months.....	1	1.51	36.0	1.9	2210.0		120.0	2450.0	26.0	62.0
37-48 months.....	1	1.51	49.0	2.45	1920.0		120.0	2040.0	37.0	63.0

DISCUSSION OF TABLE 8

Obviously in dealing with recent cases, the duration of the disease to the time of death, and the length of life following treatment, does not represent completed averages. Judgment must, therefore, be based on other sources. In the group of patients treated by rectum and urethra 45.94 per cent died during the first year after treatment, in the group treated by needles alone, 50 per cent, in the untreated group 60.79 per cent, and yet with the combined treatment only 28.78 per cent died the first year. Although sufficient time has not elapsed to give a higher percentage among the living it should be noted that the length of life following treatment already exceeds the average for patients not treated and that the living represent 54.54 per cent of patients heard from. The results argue well for the change in treatment.

TABLE 9
ONE HUNDRED SEVENTY-FIVE PATIENTS TREATED BY RADIUM ONLY

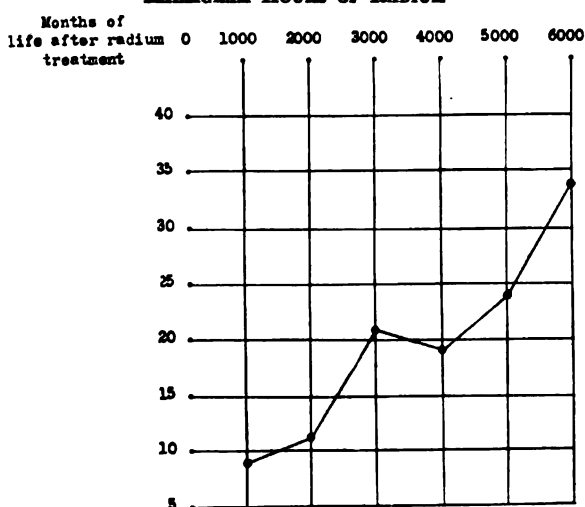
	Patients.	Per cent.	Average duration of disease, months.	Average duration of treatment, months.	Needles.	Urethra.	Rectum.	Milligram hours.	Average length of life after radium treatment, months.
Heard from.....	126		38.58	4.27	1526.65	296.76	836.65	1866.49	14.17
Dead.....	84	66.6	37.3	2.89	1183.79	301.73	1040.09	1541.16	12.83
Living.....	42	33.3	40.97	6.95	1959.73	294.43	521.3	2403.9	16.66
Patients who lived									
1-12 months.....	46	36.5	31.44	1.69	1243.86	159.33	729.94	1410.86	6.45
13-24 months.....	22	17.46	33.9	4.14	1154.71		916.26	1484.28	17.57
25-36 months.....	6	4.76	37.5	5.65		250.0	2369.0	2310.66	25.6
37-48 months.....	3	2.38	33.0	13.8	2062.0	550.0	3123.3	3994.0	41.3
Not stated.....	7	5.55							
Patients living									
1-12 months.....	20	15.87	38.9	4.6	1588.15	259.78	471.0	2332.4	8.85
13-24 months.....	16	11.76	37.33	7.97	2473.55	330.5	524.26	3094.18	18.25
25-36 months.....	1	0.79	36.0	19.0	2210.0	120.0	120.0	2450.0	26.0
37-48 months.....	5	3.96	59.0	5.9	660.0		964.0	1428.0	41.0

DISCUSSION OF TABLE 9

In Table 9 is summarized the results of all forms of radium treatment. Of the 126 patients heard from, the average duration of the disease from onset to death is 38.58 months, a little longer than may be expected if the malignancy is allowed to take its course. The average dosage was 1866.49 mg. hours and the length of life following treatment 14.17 months, only slightly longer than the average length of life of patients not treated.

A comparison of the results following radium treatment with those obtained by surgery demonstrates the superiority of the latter, for in the surgical group the disease extended 50 per cent longer, reaching, on the average, 62.36 months, and the length of postoperative life averaged ten months longer. At the end of two years 29.16 per cent of the patients treated surgically are alive and only 11.9 per cent of those treated with radium are alive. These comparisons are not wholly just, for the patients operated on represent a picked group, and in 27 per cent of them the cancer was only discovered at operation, while the patients treated by radium were unselected and the disease was advanced sufficiently to make a diagnosis. However, by examining the results from an entirely different viewpoint, namely, with reference to the size of dosages, the percentages are more encouraging. In the three groups of patients studied the length of life after radium treatment (completed cases) appears directly proportional to the dosage. That is, the average dosage for patients who lived two years was greater than for patients who lived one year, and less than for those who lived three years. That this was not accidental is borne out by grouping the patients according to the amount of radium they received instead of according to the years they have lived. The data are more accurate when taken from the completed cases, the patients who have died, for the number living includes patients who are alive because of mistaken diagnosis.

TABLE 10
FIFTY-FOUR PATIENTS
MILLIGRAM HOURS OF RADIUM



DISCUSSION OF TABLE 10

The data in Table 10 might be interpreted as meaning that because the patient lived longer he had more opportunity to receive radiation rather than that he lived because he received it. That this is fallacious is apparent from the duration of treatment, which averages between six months and one year. This relationship between dosage and prolongation of life is undoubtedly due to the fact that a more thorough radiation of the malignant growth had taken place and cell ac-

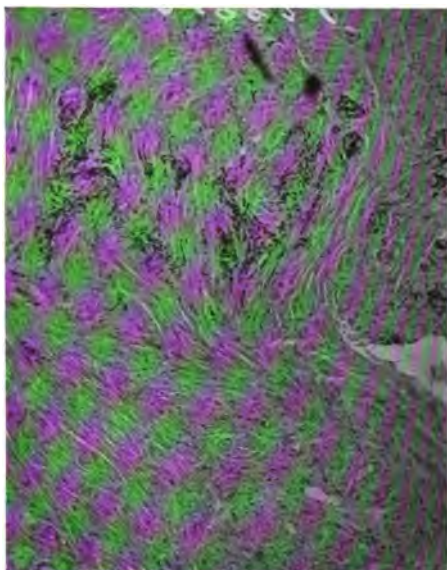


FIG. 118 (Case A219826).—Adenocarcinoma of the prostate after it had been exposed to 1,742 mg. hours of radium ($\times 50$). The last treatment had been given three months before.

had been largely destroyed. In four of the twenty-two patients who received both radium and surgical treatment the prostatectomy followed a thorough course of radium treatment, and was done to relieve the patients of urinary obstruction, not with the idea of removing the growth. Tissue in these cases yielded sections in which the end-results of radium are clearly manifest microscopically.

In Case A219826 (Fig. 118) 1,742 mg. hours of radium were given; the last treatment three months before the removal of the gland. Moderate hyaline degeneration is shown throughout the section and

marked proliferation of fibrous tissue surrounds and compresses the remaining cancer cells in interlacing fibrous bands. These malignant cells are atypical in appearance, being pressed and squeezed in distorted shapes by an ever-increasing proliferation of connective-tissue cells (Fig. 119). The reproductive function of the malignant cells is undoubtedly impaired, and if all malignant tissue can be thus affected complete cessation of the process must occur. The immediate re-

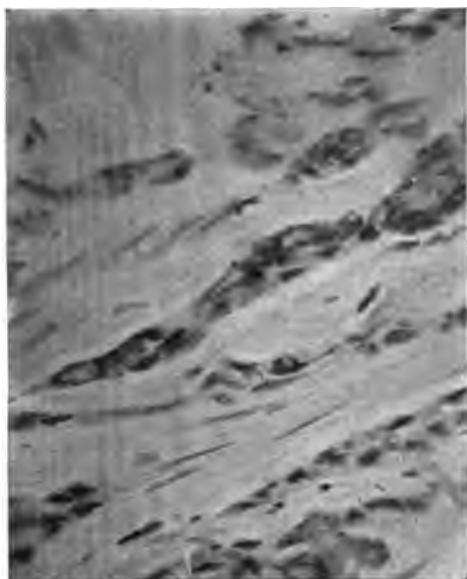


FIG. 119 (Case A219826).—Adenocarcinoma of the prostate after it had been exposed to 1,740 mg. hours of radium ($\times 500$). The last treatment was given three months before. The distorted and flattened cells indicate the extreme pressure exerted by the proliferation of fibrous tissue cells. In places this compression is so marked that only the remains of the cancer cells are seen as a few deeply staining nuclei fragments.

sults of radium treatment by needles a few days before death are shown in Figure 120. The necrotic and discolored appearance in the center of the photograph gives a clear idea of the limited extent of the radiation. Figure 121 is a photomicrograph of an area beyond the influence of the radium treatment. Typical cancer cells have replaced the normal glandular tissue. Their clear outline and marked staining qualities and the occasional mitotic figure show their viability and gives impressive evidence of malignancy. Figure 122 represents other sections from the same gland, which are taken closer to the area affected

by the radium. Many of the cells show evidence of rapid degeneration and there is a loss of the definite cell outlines of the viable cancer cells shown in Figure 121. These cells take the stain poorly and fragments of destroyed cells are seen throughout the section. The entire picture is that of cellular destruction and is in sharp contrast with Figure 121.

The microscopic findings and the marked softening and shrinking of the gland often found clinically following radium treatment

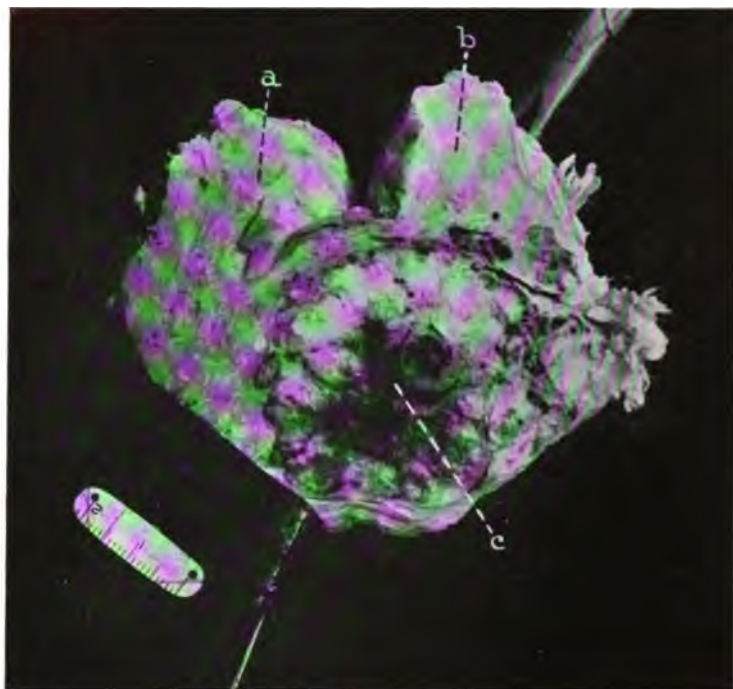


FIG. 120 (Case A332467).—Adenocarcinoma of the prostate treated thirty-two hours before death with 700 mg. hours of radium. A limited area of the carcinoma was affected and a localized necrosis resulted. (a) and (b), Lateral lobes, and (c) point of radium application. Note limited area affected by large dosage.

clear evidence that if the entire growth can be reached by the radium rays, satisfactory results will follow. Clinical findings, however, demonstrate that except in occasional cases satisfactory results have not been obtained.

The question arises, should radium treatment in cancer of the prostate be abandoned? Undoubtedly it should be abandoned in a great

many instances; after the growth has extended beyond the capsule the lymphatics are probably always involved, and the duration of the patient's life will not be altered, even if the local and original growth is softened by the treatment. Apparently much more good can be accomplished by proper care of the urinary retention by means of suprapubic drainage or daily catheterization than will be accomplished by treating the gland with radium. In a few cases a subsidence of the urinary obstruction and a marked reduction in the amount of residual urine will result, but as a rule the amount of residual urine remains

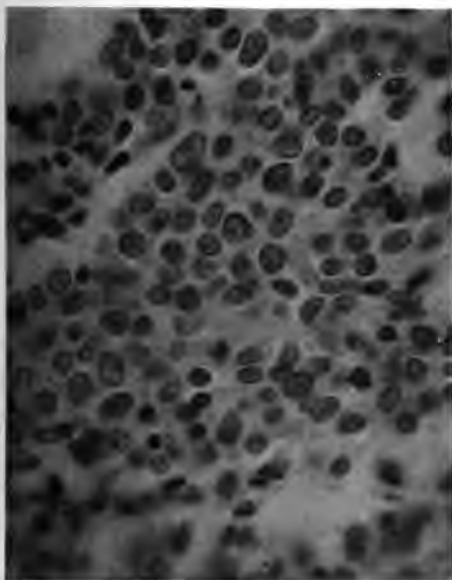


Fig. 121 (Case A332467).—Adenocarcinoma of the prostate, showing well formed and highly malignant cells unaffected by radium exposures given in other portions of the gland ($\times 500$).

unchanged and occasionally the obstruction is made greater. In the early cases, in which the malignancy is still confined within the capsule, radium should be used, but its application must be modified if better results are to be expected even in this limited group of cases.

As is apparent in Figure 120, the changes due to radium, namely, cell destruction and necrosis, are confined to a limited area. Sections of other portions of the gland (Fig. 121) show no evidence of radiation. That such necrosis occurs where radium is applied directly into the tissues has been clearly demonstrated by Bagg, who shows that the

area affected by 1 millicurie tube is approximately 1 cm., that necrosis occurs for about 1 or 2 mm., but beyond this point the malignant cells are killed for approximately 0.05 cm. Increasing the dosage from 1 millicurie to 5 millicuries does not correspondingly increase the area of affected tissue which remains approximately 1 cm. in diameter as before, but it does increase the area of necrosis around the emanating tubes, a result to be avoided since it permits nonseptic toxic absorption and is responsible for the so-termed radium reactions.

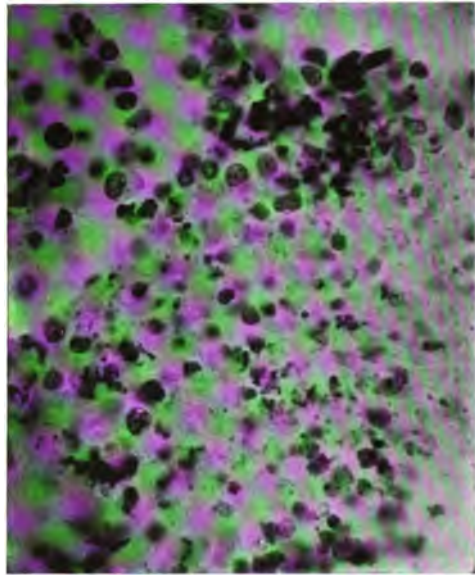


FIG. 122 (Case A332467).—Recently radiated area of adenocarcinoma of the prostate showing the effect of radium rays on the individual malignant cells ($\times 500$). Many cells have disintegrated, as shown by the loss of cell outline, poor staining quality, and masses of cell fragments.

The poor results in the past have evidently been due to the radiation of one portion of the gland, while other portions receive very little. The poor clinical results are particularly apparent in the cases in which needles alone were used, owing undoubtedly to the lack of radiation to the periphery of the growth, to which the gamma rays do not penetrate, or, if they did, were scattered and had little effect.

It is evident, therefore, that to obtain better results a greater portion of the gland must be radiated with smaller doses. In the past this has been excessively difficult and nearly impossible, for to insert ne-

more than once at a single treatment causes too great pain. An attempt was made to obviate this difficulty by inserting multiple tubes, as described by Bagg, but their exact position was uncertain and it was difficult accurately to estimate the position of the first tubes when the next one was applied. It is better not to leave emanation tubes in this deep lying gland, for if complications, such as sloughing, occurs, nature may attempt to throw off the foreign bodies rather than to encyst them. For this reason it seems that if radium needles could be used more thoroughly they would be preferable.

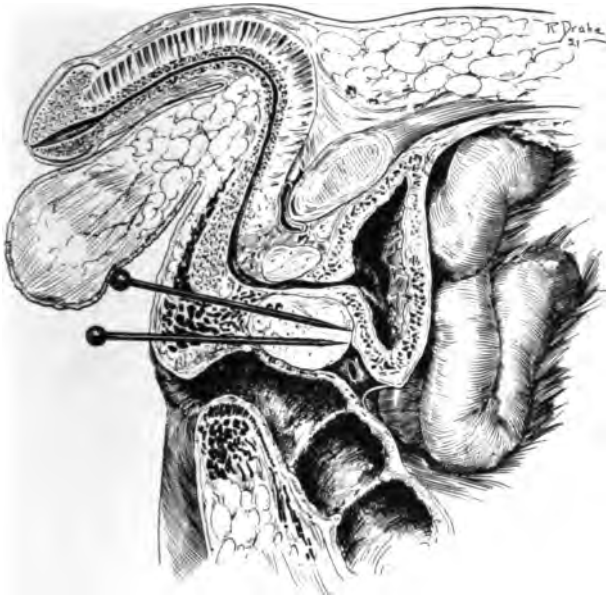


FIG. 123.—Cross-section of pelvis. Radium needles inserted into the prostate.

The possibility of now using radium needles more satisfactorily has recently been greatly favored by a method of inserting the radium needles under sacral anesthesia, as described by Scholl. He states "Nerve blocking in no part of the body offers more satisfactory or successful results than sacral anesthesia. It is not new, nor is its application to this use unusual, but its almost complete neglect indicates that its good results are not generally recognized." The absolute anesthesia obtained throughout the perineum and prostate, and the complete relaxation of the rectal sphincter make it ideal for placing needles within the prostate gland (Fig. 123), since the exact location

desired can be reached without pain to the patient. The relaxed rectal sphincter makes careful palpation of the growth possible.

The anesthetic is administered with the patient on his abdomen. After sterilizing the sacral region with iodine a 6 cm. needle with stylet is introduced through the sacral hiatus at the lower end of the sacrum into the sacral canal (Fig. 124). About 30 c.c. of a 2 per cent solution of novocain is injected while the needle is being slowly withdrawn. After this, the patient is kept in the sitting position for from ten to fifteen minutes, while the solution diffuses through the sacral nerve sheath. This diffusibility is greatly increased if sodium carbonate is added.

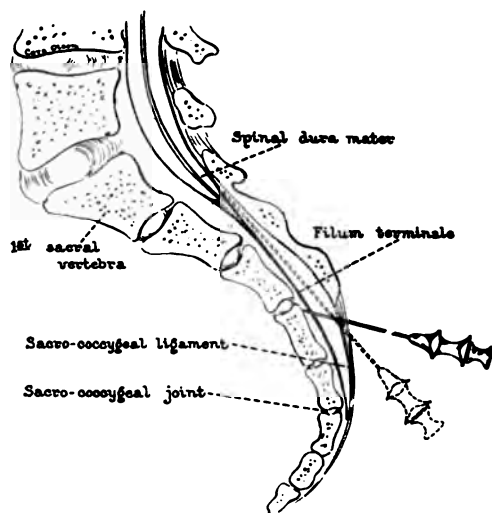


FIG. 124.—Cross-section of sacrum. Sacral canal and point of insertion of needle. novocain is given outside the spinal dura mater.

the novocain. The formula is as follows: Novocain 0.6 gm., sodium carbonate 0.15 gm., sodium chlorid 0.1 gm. added to 30 c.c. of freshly boiled distilled water; this gives a sterile 2 per cent solution of novocain in normal salt solution.

The anesthesia is complete and commences in about four minutes at the anosacral area, the exact location at which the needles are inserted (Fig. 125). The anesthesia may be repeated at any time and the position of the needles in the gland changed, so that new areas may be radiated. After the second injection the anesthesia is much more profound and lasts from five to eight hours, permitting a third shift of the radium-containing needles and giving the patient a period of

and freedom from pain during the procedure. This anesthetic has been used in more than 100 instances with complete satisfaction. Patients are no longer reluctant to take a second treatment and the increased ease with which the needles are applied, owing to the complete relaxation of the rectal sphincter, adds greatly to the exactitude of the procedure, and before the completion of the treatment all parts of the gland will have been radiated.

The entire treatment is given within a few days and the patient need not return for subsequent treatments. It is scarcely necessary to call attention to the advantages gained by this method. There is no

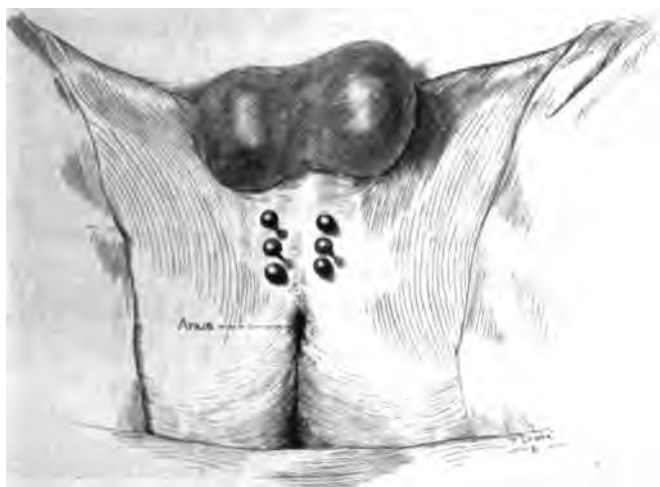


FIG. 125.—Six radium needles inserted into the perineum.

opportunity for growth of the untreated portions of the gland between treatments. Necrosis does not occur, since fibrous tissue which greatly reduces the blood supply has not formed as the result of previous radium treatments.

SUMMARY

1. The average duration of cancer of the prostate, if untreated, is approximately three years.
2. Roentgenograms show that metastasis to the bone occurs in about one-third of the cases of cancer of the prostate.
3. Metastasis from atypical carcinoma of the prostate, in which the cells, because of their tendency to early metastasis, produce only slight local enlargement, may be frequently mistaken for Paget's disease.

4. The clinical study of these cases demonstrates that in order to treat successfully cancer of the prostate with radium it is necessary to use in the aggregate large doses (3,000 to 4,000 mg. hours), exposing all parts of the gland to comparatively small doses.

5. It is demonstrated that the increased duration of life following radium treatment in cases of cancer of the prostate is in direct proportion to the amount of radiation applied.

6. No one method of application radiates all portions of the gland.

7. The malignant gland must be radiated by urethral and rectal exposures, and by needles inserted directly into the neoplasm in order to produce complete radiation of all portions.

8. It is demonstrated microscopically that large doses of radium placed directly into the gland affect only a limited area; this is substantiated by the clinical findings, which prove that the course of the disease after such treatments is but slightly affected.

9. In the parts of the gland affected by the radium fibrous tissue is produced which enmeshes and compresses the cancer cells preventing their further proliferation. If this process could be brought about in the entire growth complete cessation of the disease would result.

10. Sacral anesthesia is a useful adjunct in the application of radium needles, making it possible to place the radium accurately and to change the position of the needles without pain; thus a more thorough radiation of the gland is accomplished.

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SURGERY OF THE PROSTATE*

VERNE C. HUNT

Lesions of the prostate show few variations in type. Probably not more than one-half are surgical. As shown by Judd and Crenshaw in a review of all patients seen in the Mayo Clinic for a period of eight and one-half years in whom symptoms were produced by prostatic lesions, only 42 per cent were surgical; these were subjected to operation.

Prostatitis is of two distinct types. The acute form, practically always due to gonorrheal infection, occurs most often in young men, and because it usually responds to nonsurgical treatment is very seldom treated surgically. Chronic prostatitis may be the result of gonorrheal infection in youth, but may give rise to few symptoms until later in life. In a recent review of 856 cases in which prostatectomy was performed the gland was of the chronic fibrous type in fifty, without adenomatous hypertrophy; in forty-eight prostatitis was the primary condition, and the glands contained a few small adenomas, while in fifty-six marked prostatitis was associated with primary adenomatous hypertrophy. Chronic prostatitis, with little enlargement of the gland, is capable of producing all the symptoms of adenomatous hypertrophy; that is, frequency, difficulty, and incomplete emptying of the bladder, with the residual urine at times amounting to the entire capacity of the bladder, and in some cases, acute retention. The marked fibrosis in this type of prostatitis and the absence of cleavage planes correspond to those changes occurring in other parts of the body following infection, which would indicate that infection must play an important part in the etiology of urinary disturbances in the presence of this type of gland.

Prostatic abscesses, single or multiple, quite often occur secondary to the acute infections of the prostate during the course of venereal disease. Few, however, become surgical, for they usually point and drain through the urethra. As a surgical condition, therefore, prostatic abscesses are of relatively slight importance.

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Carcinoma of the prostate is found in 15 per cent of the patients with symptoms of prostatic obstruction. Unfortunately, the onset of these symptoms is gradually insidious and, as is seen in malignant disease elsewhere in the body, the symptoms are usually manifest only when the disease has advanced locally to the paraprostatic tissues and the bladder, and remotely by metastasis. Surgery has seldom been productive of permanent good results in these cases. Bumpus, in his analysis of 362 cases of carcinoma of the prostate observed in the Mayo Clinic, found that remote metastasis had occurred in 21.8 per cent. This finding led to a more careful examination and search for metastasis in a later series, and metastasis to the bones was revealed in 30.3 per cent of 135 patients who were subjected to roentgen-ray examination. The bones most frequently involved were those of the pelvis and spine, and the femur. Metastasis to the lungs occurred rarely in the late stages of the disease; it was found in the regional glands in 10.2 per cent of 362 cases.

Metastasis found at the first examination immediately removes the patient from the surgical field approximately 40 per cent of all cancers of the prostate. The local advancement of the disease with its early involvement of the bladder and of surrounding structures, and the discouraging results following the radical operation have also excluded practically all cases without metastasis from surgical treatment except a small percentage in which palliative suprapubic drainage is necessary. Bumpus states that of 146 patients with carcinoma who were subjected to prostatectomy 80 per cent died within two years after operation, and of sixty-six patients who lived more than three years only seven were alive after seven years.

Benign adenomatous hypertrophy is by far the most frequent surgical lesion of the prostate. It occurs most often late in life. Only 5 per cent of a series of 856 patients were under fifty. Twenty-eight per cent were between the ages of sixty and sixty-five, and 83 per cent were in the sixth and seventh decades.

It has been pointed out that the size of the gland bears no relation to the amount of disturbance it may produce. In 9.7 per cent enlargement of the gland was graded 1 (on a scale of 1 to 4), in 48.45 per cent it was graded 2, in 33.95 per cent it was graded 3, and in 7.8 per cent it was graded 4. A slightly enlarged gland may produce marked obstruction with the residual urine amounting to the full capacity of the bladder, while a huge intra-urethral and intravesical gland may

produce mechanical interference with complete emptying of the bladder at urination, or any of the other manifestations of prostatic disease, and may be spoken of as the "silent" prostate.

The indications for or against operation in benign hypertrophy of the prostate are based on the amount of disturbance the gland is producing and the general condition of the patient. A large prostate, found in the routine examination, if unproductive of frequency, difficulty, pain, hematuria, or incomplete emptying of the bladder with resultant residual urine, is of itself usually not surgical. However, when any or all of these symptoms are present as the result of adenomatous hypertrophy of the gland, irrespective of its size, the condition is surgical in the absence of general contraindications.

The effect of enlargement of the gland on the urinary tract and on the general condition of the patient forbids immediate operation in a large percentage of these cases. When symptoms of prostatic obstruction appear there is nearly always incomplete emptying of the bladder with resultant persisting and increasing amounts of residual urine, but in 9.6 per cent of the cases in our series in which prostatectomy was performed there was no residual urine. In 37 per cent it was but two ounces or less, and in 16.6 per cent the amount equaled that of the capacity of the distended bladder, the patient voiding simply the overflow. With the advent of the residual urine and its back pressure on the kidneys, and the occurrence of secondary infection, pyelonephritis, supervenes with diminished renal function of variable degree, depending on the amount of residual urine and the length of time it has been present. The finding of residual urine so constantly in prostatic obstruction, and the associated pyelonephritis makes it necessary that these patients be considered at least potentially, if not actually uremic. Recognition and treatment of the actual or potential uremia preliminary to operation is a most important feature in the successful management of cases of benign hypertrophy of the prostate. In many instances if large amounts of residual urine have been present for a long time, renal function is markedly diminished, as is shown by absence of return of the dye in two hours by the phenolsulphonaphthalein test, and by retention of urea to 100 mg. or more for each 100 c.c. of blood. There is often a severe cystitis, and 10 per cent of our patients have had associated single or multiple bladder stones. Removal of the residual urine and prolonged constant drainage and irrigation of the bladder are means of improving the renal function and general con-

dition of the patient. This improvement governs the length of time preliminary drainage should be maintained. It is our practice to institute drainage of the bladder in all cases when the residual urine is more than two ounces. This may be accomplished by suprapubic drainage or by a permanent indwelling catheter. The latter is preferable in most cases. Suprapubic drainage is reserved for patients who do not tolerate the urethral catheter nor improve by its use, for those in whom the residual urine is residual, with marked renal insufficiency and symptoms of uremia, for those with severe cystitis, and for those in whom there are single or multiple bladder stones. Patients who have had more than two ounces of residual urine and little or no renal insufficiency have been subjected to prostatectomy without preliminary treatment. This comprises approximately 25 per cent of the cases. About 50 per cent have been prepared for prostatectomy by permanent urethral catheter. The percentage in the latter group has recently been increased by confining to bed those patients who are otherwise intolerant of the urethral catheter, and by the utilization of the method of gradual decompression of the bladder, as described by Van Zwalenburg for patients with chronic retention and great distention of the bladder who were formerly subjected to suprapubic drainage preliminary to prostatectomy.

There has been much discussion and difference of opinion on the effect of sudden emptying of a distended bladder. Some observers contend that sudden withdrawal of all the urine from a distended bladder is a dangerous procedure and precipitates uremia, while others have seen no ill effects. The operation of suprapubic drainage and immediate withdrawal of all urine in the presence of chronic retention to the entire bladder capacity and marked renal insufficiency is without danger, but is accompanied by a variable mortality rate. It would seem, from our observation of patients who have heretofore been subjected to suprapubic drainage, and of patients with similar cases in which decompression has been done in recent months by Van Zwalenburg's method without mortality, that the sudden withdrawal of the urine is a factor in precipitating uremia. The gradual decompression method has the distinct advantage of accomplishing all that suprapubic drainage accomplishes in most of the cases, and of increasing the percentage of cases in which the one-stage prostatectomy may be performed with safety.

The anatomic location of the prostate offers two methods of

proach for surgical removal, the perineal and the suprapubic trans-vesical routes. Each method has its advocates and some surgeons employ the combined perineal and suprapubic approach. The perineal method possesses the disadvantages of possible operative injury to structures, resulting in the frequent postoperative complications of incontinence through injury to the external vesical sphincter, and of recto-urethral fistula through accidental opening of the rectum during the operation. The adoption of the suprapubic route by surgeons who have had experience with the perineal operation seems to indicate that these complications outweigh the advantages of the operation. The suprapubic route approaches immediately the part of the gland; that is, the median and lateral lobes, in which adenomatous hypertrophy occurs, and affords an opportunity thoroughly to explore the bladder, and to treat frequently associated lesions such as calculi and diverticula, and, rarely, carcinoma of the bladder.

Some surgeons employ the two-stage suprapubic operation in all cases, and others employ the one-stage operation entirely. An intermediate course is taken at the Mayo Clinic; the one-stage operation is preferred after preliminary preparation by urethral drainage of the bladder. The percentage of cases in which the one-stage operation may be performed with safety has been increased by the use of Van Zwalenburg's method of decompression. In the past the foremost argument in favor of the two-stage suprapubic operation has been the elimination of infection. However, the foul, sloughing wounds and infections in the prevesical space following the one-stage operation have practically disappeared and are now rarely seen. This absence of infection may be accounted for by the fact that formerly prostatectomy was performed with little or no preparation of the urinary tract by urethral drainage and irrigation of the bladder, and the operation was conducted in the presence of serious infection. The recognition in recent years, preoperatively or at operation, of diverticula of the bladder has eliminated a postoperative source of infection. The improved technical accuracy of the one-stage operation has been productive of better wounds, less infection, and a shorter convalescence. The two-stage operation necessitates the blind enucleation of the gland and, through the lack of facility to perform the operation accurately under the eye, to control bleeding, and so forth, directly opposes the general principles of surgery, with little or nothing to be gained by the patients through its use. The operation has been acclaimed ideal for the patient who is

a poor risk, in that it is a divided procedure, is less time consuming requires a short anesthesia. These reasons do not seem to apply at the present time. The progress made in surgery has improved the technical details of the operation of prostatectomy, and has presented us with anesthetics other than ether which exclude the time element as an important factor.

The choice of anesthetic is of great importance in prostatic surgery. It has always been desirable when employing ether to use a minimum amount and to perform the operation as rapidly as possible, on account of the depressing effect of ether on the kidneys. Spinal anesthesia has been used largely throughout the country, but it has not been without accompanied by danger. However, in our experience, Labat's method of employing this type of anesthesia has reduced its danger to a minimum. It has been devoid of complications or ill effects. The combined technique of sacral and abdominal infiltration with novocain affords an ideal anesthesia. For the past six months all operations for removal of the prostate have been performed by the use of one or the other of these anesthetics. They eliminate the time element from the operation and avoid the wide open exposure of the bladder, affording thorough exploration and visual removal of the gland, with accurate control of the bleeding. For the patient who is a poor risk exposure and accuracy in the operation are exceedingly important, for he is intolerant to postoperative bleeding.

Important details in the one-stage operation are: (1) careful suturing of the bladder neck, which is the source of most of the bleeding; (2) control of the bleeding from the interior of the prostatic capsule; (3) accurate closure of the bladder. Various methods have been devised to control the bleeding from the interior of the prostatic capsule. The Pilcher bag is being used successfully in the Clinic for this purpose. By its use all of the suprapubic tubes may be removed from the bladder the day following operation, and a urethral catheter inserted, which in the majority of cases allows the wound to heal by first intention, and no urinary drainage suprapubically after the removal of the bag. Convalescence is materially shortened in these cases.

The mortality rate in the operation of prostatectomy has been greatly reduced during the past few years. This has been due to the recognition that these patients are potentially uremic, and that treatment of the actual or potential uremia is necessary before operation, (2) the increased technical accuracy of the operation, and (3) the elimination of ether as the anesthetic. Greater care in the selection

cases, more accurate determination of when the patient is ready for operation, and the use of anesthetics that do not depress the kidneys should reduce the mortality rate to approximately 1 per cent. Suprapubic prostatectomy is productive of excellent functional results and is devoid of any of the complications of the perineal operation. The results of operation have recently been determined by questionnaires sent to 614 patients. Ninety-four and five-tenths per cent report that they are cured or markedly improved.

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CANCER OF THE BREAST: THE RESULTS OBTAINED IN 218 OPERATIONS*

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I have recently studied in detail the histories of the 246 patients operated on for cancer of the breast in the Mayo Clinic during the years 1911, 1912, and 1913. I was fortunate in having at my disposal detailed histories, complete pathologic reports, and good descriptions of the operative procedures, and after much effort fairly accurate results of the results were obtained in 218 of the 246 patients.

The study of these cases impresses one that little more can be expected so far as results are concerned by a change in the present operative technic. The recurrences were mostly in late cases, evidence because cancerous tissue was left in regions inaccessible to the knife, while the highest percentage of cures and the infrequent recurrences occurred in patients operated on early in the course of the disease before glandular involvement could be demonstrated. The end-results obtained are probably better than those obtained from operation on any other type of cancer with the exception of the basal-cell epidermoid, sarcomas of the skin and cancers of the parotid gland and of the lip.

Only a comparatively short time has elapsed since surgeons regarded the condition of cancer of the breast with great pessimism. Practically all persons with the disease died and it was generally believed that the condition was a systemic instead of a local disease. Too much credit cannot be given to the surgeons who have contributed toward the perfection of the operation as it is now generally performed, and have made it possible by surgery to achieve results as those now obtained in a formerly almost hopeless condition. When the public is better educated with regard to the necessity of seeking surgical aid early for all breast tumors and when it is generally recognized by the entire medical profession that the day of waiting for breast tumors is past, it seems likely that as high as 75 or 80 per cent of patients with cancer of the breast should obtain from five- to ten-year cures.

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TYPE OF OPERATION

The operation usually performed is based largely on the knowledge of the lymphatic supply of the breast. The lymphatics draining the breast largely accompany the blood vessels and may be expected to be found along the course of the large vessels supplying the breast. These empty largely into the group of lymphatics lying along the axillary vein and those accompanying the vessels which perforate the chest wall (branches of the internal mammary and intercostal arteries). Lymphatics have also been found running from the upper inner quadrant of the breasts directly into the supraclavicular regions; from the lower inner quadrant of each breast into the opposite axilla; and to the epigastric region and thence into the abdominal cavity along the round ligament of the liver. It does not seem practical to remove the supraclavicular glands in all patients operated on for cancer of the breast and it is doubtful that much good would be accomplished by such a procedure. It is also impossible to remove all of the lymphatics accompanying the perforating branches of the internal mammary and intercostal arteries. Recurrences in the opposite axilla, except in advanced cases, are extremely rare; probably they are usually due to the fact that the disease has recurred at some point which is drained by lymphatics which empty into this axilla. For these reasons operative measures are necessarily limited largely to the wide removal of the skin, subcutaneous fat, superficial and deep fascias, and the axillary lymphatics; the other tissues which it would be of advantage to remove are beyond the scope of surgery. When complete axillary dissections are made, even in cases in which the axillary glands are involved, recurrences seldom occur in the axilla. In the series studied local recurrences are known to have occurred in only 10.5 per cent of the patients in whom no glandular involvement could be demonstrated at the time of operation. In the forty-six cases with local recurrences the glands were involved at the time of operation in 80.4 per cent, which tends to show that it is in the late cases that local recurrences are likely to develop.

The usual type of operation was employed in our series of cases. A wide removal of the skin and subcutaneous fat was effected and both pectoral muscles removed. An extensive dissection of the subscapular and axillary lymphatics was made, the glands and fascia in the deep infraclavicular triangle and a portion of the fascia covering

the upper portion of the rectus muscle were removed. The skin incision was a slight modification of the Rodman incision, made it possible to bring the skin edges in practically all cases.

The function of the arm following such operations is almost perfect. It seems to be impaired only in those patients who are timid and fail, because of pain and discomfort, systematically to work the shoulder joint following operation. The scar of such an incision does not involve the axilla, and this region, therefore, is free from pain.

The results obtained in the 218 cases will be discussed under various headings:

GLANDULAR INVOLVEMENT

The axillary glands were found to be involved in 60.5 per cent of the cases, which clearly demonstrates that the majority of patients with cancer of the breast come to operation in a late stage of the disease. Of eighty-six patients operated on before the glands were involved, 64 per cent are alive from five to eight years after operation, with known recurrences in only six. Of 132 patients in whom the glands were found to be involved at the time of operation, 19 per cent are alive from five to eight years after operation and only three of these are known to have recurrences. Of the 218 patients grouped collectively with reference to glandular involvement, 36.7 per cent are alive from five to eight years after operation, with known recurrences in nine. The percentage of five-year cures obtained in this series is almost identical with that obtained in a previous group of 510 cases reported by Judd and me in 1914, in which 39.8 per cent were five-year cures, and no doubt that it is a very fair estimate of the cures to be expected five years after operation. The percentages of five-year to eight-year cures in patients operated on with glandular involvement and of those operated on before the glands were involved are strikingly different, 19 per cent in the former and 64 per cent in the latter. The involvement or noninvolvement of the glands seems to be the greatest factor in the prognosis following operation (Table 1).

In studying the effect of glandular involvement on the prognosis, a very interesting fact was noted, which allows one to determine very accurately at the time of operation the number of patients in a series who will be likely to die within five years and those who will be likely to live five years; that is, it was found that a death was expected to occur within five years for each patient with the glands

TABLE 1
RESULTS OBTAINED IN 218 CASES IN WHICH OPERATION WAS PERFORMED

	Alive five to eight years after operation.	Dead.
Patients without glandular involvement 86 (39.5 per cent)	55 (63.9 per cent)*	31 (36.1 per cent)
Patients with glandular involvement 132 (60.5 per cent)	25 (18.9 per cent)†	107 (81.1 per cent)
Total, 218	80 (36.7 per cent)	138 (63.3 per cent)

* Six recurrences.

† Three recurrences.

Total nine.

involved at the time of operation. While this rule is not absolute it was found to be so nearly true in studying the prognosis from so many standpoints when the question of glandular involvement was considered as to make it a good and fairly accurate working rule. For instance, the glands were found to be involved in 60.5 per cent of our patients, and at the end of five years 61 per cent were dead; the glands were not involved in 39.5 per cent of the patients and 39 per cent were alive. In eighty-six patients of the entire series no glandular involvement could be demonstrated and eighty-five patients of the entire series were alive at the end of five years. The glands were found to be involved in 132 patients and there were 133 deaths in the series at the end of five years. From almost any standpoint that this rule was applied it was found to be correct within a very small percentage. All of the patients with glandular involvement do not die, but the number who die when the glands are not involved at the time of operation seems to very closely equalize the number who live when the glands are found to be involved (Table 2).

TABLE 2

FREQUENCY OF GLANDULAR INVOLVEMENT IN CARCINOMA OF THE BREAST AND ITS EFFECT ON PROGNOSIS

Patients.....	218
Glands involved.....	132 (60.5 per cent)
Glands not involved.....	86 (39.5 per cent)
Patients alive from five to eight years after operation.....	80
Glands involved.....	25 (31.2 per cent)
Glands not involved.....	55 (68.8 per cent)
Patients known to be dead.....	138
Glands involved.....	107 (77.5 per cent)
Glands not involved.....	31 (22.5 per cent)

SEX

All the patients in the series were females, so it was impossible to make a comparison of the results obtained in the two sexes. However, the group clearly demonstrates, as have other statistics, the great frequency of cancer of the breast in females compared with males.

AGE

The highest percentage of deaths occurred in the youngest and oldest patients, but in these the glands were involved in from 70 to 75 per cent, and this and not the age probably accounts for the high mortality in these groups. One hundred eight of the patients were over fifty, and 110 were under fifty. Forty-one and seven-tenths per cent of the patients over fifty are alive from five to eight years following operation, while only 31.8 per cent of the patients under fifty are alive for a corresponding length of time. Twenty-five and four-tenths per cent of the patients over fifty and thirteen per cent of those under fifty who had glandular involvement at the time of operation are alive. The percentage of chance for cure seems definitely higher in patients over fifty. Whether this was due to the age or to the cessation of menstruation in these cases could not be determined, as the results were almost similar for women who had passed the menopause and for those who were over fifty years. The highest percentage of cures occurred in the fifty-nine patients between fifty and sixty; 71 per cent of this group without glandular involvement are alive five to eight years after operation and only 64 per cent of all patients without glandular involvement are alive; 28.6 per cent of this group with glandular involvement at

TABLE 3
PERCENTAGE OF DEATHS UNDER AND OVER "FIFTY YEARS"

	Cases.	Alive from five to eight years after operation.
Under fifty.....	110 (50.5 per cent)	
With glandular involvement.....	69 (62.7 per cent)	9 (13.0 per cent)
Without glandular involvement.....	41 (37.3 per cent)	26 (63.4 per cent)
		35 (31.8 per cent)
Over fifty.....	108 (49.5 per cent)	
With glandular involvement.....	63 (58.3 per cent)	16 (25.4 per cent)
Without glandular involvement.....	45 (41.7 per cent)	29 (64.4 per cent)
		45 (41.7 per cent)

the time of operation are alive from five to eight years after operation, and only 19 per cent of all patients with glandular involvement are alive. Also only 47.4 per cent of the patients from fifty to sixty years had glandular involvement, while the percentage of the patients of the entire series with glandular involvement was 60.5 (Table 3).

MENSTRUATION

One hundred eleven patients of the series had passed the menopause at the time of operation; 107 were still menstruating. There is little difference in the percentage of cures in these two groups, 38.7 per cent in the former and 34.6 per cent in the latter are alive from five to eight years after operation. On the other hand, twice as many patients with glandular involvement at the time of operation who had passed the menopause are alive from five to eight years after operation as patients with glandular involvement who were still menstruating (24.6 and 12.7 per cent) (Table 4).

TABLE 4

RESULTS OBTAINED IN PATIENTS WHO WERE MENSTRUATING AND IN THOSE WHO HAD PASSED THE MENOPAUSE

	Cases.	Alive from five to eight years after operation.
Patients who had not passed the menopause.....	107 (49.1 per cent)	
With glandular involvement.....	63 (58.9 per cent)	8 (12.7 per cent)
Without glandular involvement.....	44 (41.1 per cent)	29 (65.9 per cent)
		37 (34.6 per cent)
Patients who had passed the menopause..	111 (50.9 per cent)	
With glandular involvement.....	69 (62.1 per cent)	17 (24.6 per cent)
Without glandular involvement.....	42 (37.9 per cent)	26 (61.9 per cent)
		43 (38.7 per cent)

CHILD-BEARING

Fifty-five of the patients had never borne children; 157 are known to have borne one child or more. Forty-three and six-tenths per cent of the former and 35 per cent of the latter are alive from five to eight years after operation. If only the patients whose glands were not involved are considered, 75 per cent of the former and 58.3 per cent of the latter are found to be alive. The glands were found to be involved

slightly more frequently in patients who had borne children than in those who had not (61.8 and 56.4 per cent).

Pregnancy.—Two patients had carcinoma of the breast during pregnancy; one died two years after operation and the other five years after.

Lactating breasts.—Four patients had carcinoma in lactating breasts. All died, although the glands were involved in only two. They lived one, two, three, and five years after operation respectively.

ULCERATING GROWTHS

In twenty cases the carcinomas were ulcerating at the time of operation. These, of course, were extremely late cases. The glands were involved in 90 per cent and seventeen (85 per cent) of the patients are dead.

LOCATION OF THE GROWTH

The growth was located in the upper and outer halves of the breast more than twice as often as in the lower and inner halves, 46.8 per cent in the upper half, 45.8 per cent in the outer half, 20.7 per cent in the lower half, and 17.4 per cent in the inner half. Involvement of the glands occurred most often in growths located in the outer half (64 per cent); the involvement was about equal in the upper and lower halves (about 55 per cent) and least in the inner half (39.5 per cent). The growth was found about three times as often in the upper outer quadrant of the breast as in any other quadrant; it was located with about equal frequency in the upper inner and lower outer quadrants, and least frequently in the lower inner quadrant, five times less frequently than in the upper outer quadrant. The glands were found to be involved with about equal frequency (about 64 per cent) in cases in which the growth was located in the upper and lower outer quadrants; they were involved in 50 per cent when the growth was located in the lower inner quadrant, and in only 31.6 per cent when the growth was in the upper inner quadrant. Fifty-two and six-tenths per cent of the patients with the growth in the upper inner quadrant were alive from five to eight years after operation, 40.3 per cent with the growth in the upper outer quadrant, 36.4 per cent with the growth located in the lower outer quadrant, and 25 per cent with the growth in the lower inner quadrant. The mortality was highest in cases in which the growth was in the lower inner quadrant and the percentage of cures was highest in cases

in which the growth was in the upper inner quadrant. In the diffuse growths (sixteen), that is, the growths involving almost the entire breast, or the type which apparently develops on a preëxisting diffuse mastitis, the glands were involved in fifteen (93.7 per cent) of the

TABLE 5

FREQUENCY OF INVOLVEMENT OF RIGHT AND LEFT BREASTS AND THE RESULTS OBTAINED
BASED ON THE BREAST INVOLVED

	Cases.	Alive from five to eight years after operation.
Right breast.....	103 (47.2 per cent)	
With glandular involvement.....	43 (41.7 per cent)	22 (51.2 per cent)
Without glandular involvement.....	60 (58.3 per cent)	11 (18.3 per cent)
		33 (32.0 per cent)
Left breast.....	113 (51.8 per cent)	
With glandular involvement.....	42 (37.2 per cent)	33 (78.6 per cent)
Without glandular involvement.....	71 (62.8 per cent)	14 (19.7 per cent)
		47 (41.7 per cent)

Both breasts were involved in two patients; both are dead.

TABLE 6

LOCATION OF CANCER IN DIFFERENT HALVES OF THE BREAST

	Cases.	Alive from five to eight years after operation.
Outer half.....	100 (45.8 per cent)	
With glandular involvement.....	64 (64.0 per cent)	16 (25.0 per cent)
Without glandular involvement.....	36 (36.0 per cent)	23 (63.9 per cent)
		39 (39.0 per cent)
Upper half.....	102 (46.0 per cent)	
With glandular involvement.....	57 (55.9 per cent)	18 (31.6 per cent)
Without glandular involvement.....	45 (44.1 per cent)	27 (60.0 per cent)
		45 (44.1 per cent)
Lower half.....	45 (20.7 per cent)	
With glandular involvement.....	25 (55.5 per cent)	5 (20.0 per cent)
Without glandular involvement.....	20 (44.5 per cent)	13 (65.0 per cent)
		18 (40.0 per cent)
Inner half.....	38 (17.4 per cent)	
With glandular involvement.....	15 (39.5 per cent)	3 (20.0 per cent)
Without glandular involvement.....	23 (60.5 per cent)	14 (60.9 per cent)
		17 (44.7 per cent)

TABLE 7
LOCATION OF CANCER IN DIFFERENT QUADRANTS OF THE BREAST

	Cases.	Alive from five to eight years after operation.
Upper outer quadrant.....	62	
With glandular involvement.....	40 (64.5 per cent)	13 (32.5 per cent)
Without glandular involvement.....	22 (35.5 per cent)	12 (54.5 per cent)
		25 (40.3 per cent)
Upper inner quadrant.....	19	
With glandular involvement.....	6 (31.6 per cent)	1 (16.7 per cent)
Without glandular involvement.....	13 (68.4 per cent)	9 (69.2 per cent)
		10 (52.6 per cent)
Lower outer quadrant.....	22	
With glandular involvement.....	14 (63.6 per cent)	2 (14.3 per cent)
Without glandular involvement.....	8 (36.4 per cent)	6 (75.0 per cent)
		8 (36.4 per cent)
Lower inner quadrant.....	12	
With glandular involvement.....	6 (50.0 per cent)	2 (33.3 per cent)
Without glandular involvement.....	6 (50.0 per cent)	1 (16.7 per cent)
		3 (25.0 per cent)
Centrally located.....	26	
With glandular involvement.....	18 (69.2 per cent)	1 (5.5 per cent)
Without glandular involvement.....	8 (30.8 per cent)	6 (75.0 per cent)
		7 (26.9 per cent)
Diffuse.....	16	
With glandular involvement.....	15 (93.7 per cent)	0
Without glandular involvement.....	1 (6.3 per cent)	0
Not mentioned.....	4	
With glandular involvement.....	1 (25.0 per cent)	0
Without glandular involvement.....	3 (75.0 per cent)	0

patients at the time of operation; all of the patients with diffuse growths are dead. When the growths were centrally located (twenty-six), that is, around the nipple, the glands were involved in eighteen (69.2 per cent) of the patients; seventeen (94.5 per cent) of the latter are dead. However, of the patients with centrally located tumors whose glands were not involved eight (75 per cent) are alive from five to eight years after operation (Tables 5, 6, and 7).

Attachment of the growth to the skin.—In 38.5 per cent of the 218 cases the growth was mentioned in the histories as being attached to the skin. The glands were involved in only 53.6 per cent of these

patients and 29 per cent of these with the glands involved are alive from five to eight years after operation. In 61.8 per cent of 110 patients in whom the growth was not mentioned as being attached to the skin the glands were involved and only 16.2 per cent of these patients with glandular involvement are alive. The prognosis seemed better in the series in which the growth was attached to the skin. In such cases the growth is usually found in the superficial portion of the breast; such growths attract attention earlier and earlier operation is sought. On the other hand, the prognosis seems less favorable if the growth is not attached to the skin, probably on account of the fact that the growth is more deeply placed and often not recognized until the glands are involved, or that the lymphatic drainage from the deeper portions of the breast is more active than that in the periphery.

LOCATION OF RECURRENT GROWTHS

In ninety-seven patients we have a fair idea with regard to the location of the recurrences. The glands were involved in 75.2 per cent. In the ninety-seven patients recurrences had occurred locally, that is, around the region of the operative scar, or locally and in some other region at the same time in 47.4 per cent. The glands were involved at the time of operation in 80.4 per cent of the patients in whom local recurrences had occurred, a fact which would tend to show that local recurrences are to be expected largely in late cases. One hundred and thirty-two patients had involvement of the glands at the time of operation; local recurrences are known to have occurred in thirty-seven (28 per cent). In eighty-six patients no glandular involvement was demonstrated at the time of operation; local recurrences are known to have occurred in nine (10.5 per cent) of these. Evidences of metastasis in other regions were present in all except eighteen of the patients with local recurrences.

In twenty-one (9.6 per cent of the entire series) or 21.6 per cent of the ninety-seven patients the metastasis was in the lung, pleura, or mediastinum. The glands were involved in 71.4 per cent of these.

In seventeen (7.8 per cent of the 218 cases) or 17.5 per cent of the ninety-seven patients recurrences occurred in the bones; in thirteen cases the involvement was in the spine; three had recurrences in the femur and in one case the spine and femur were both involved. The glands were involved in 64.7 per cent of these cases.

Intra-abdominal recurrences were found in eleven patients (5 per cent of the entire series) or 11.3 per cent of the ninety-seven cases. The glands were involved in 81.8 per cent of these.

Three patients (1.4 per cent of the total number) or 3.1 per cent of the ninety-seven had metastasis in the brain. The glands were involved in only one of these.

In six patients the condition recurred in the other breast. It was impossible to determine whether these recurrences were direct metastasis or whether a primary carcinoma had developed in the other breast.

RESULTS OF OPERATIONS

Primary mortality.—Only one patient in the series died in the hospital, an immediate mortality of 0.4 per cent. This patient died of pneumonia and nephritis ten days after operation.

CAUSE OF DEATH IN PATIENTS KNOWN TO BE DEAD

One hundred four (75.3 per cent) of the 138 patients died from recurrences of the cancer; of twenty-three we have no knowledge of the cause of death or whether the cancer recurred; eleven patients died supposedly from disease other than cancer and without a recurrence, one of pneumonia, one of influenza, one of pernicious anemia, one of apoplexy, one of Bright's disease, one of cholecystitis, four of heart disease, and one of gangrene of both legs (thrombosis?). Nine of these patients were over fifty and two were under fifty. While these patients were recorded as having died from cancer, they probably should have been deducted from the deaths, as insurance statistics show that about the same percentage of persons of these ages die during this period of time (Table 8).

DURATION OF LIFE FOLLOWING OPERATION IN PATIENTS WHO DIED

Six (2.7 per cent) of the 218 patients died within six months following operation. By the end of the first year forty-six (21.1 per cent) were dead; by the end of two years seventy-six (34.9 per cent); by the end of three years ninety-two (42.2 per cent); by the end of four years 107 (49.1 per cent), and by the end of five years 120 (55 per cent); only five (2.3 per cent) died after five years. In thirteen cases (5.9 per cent) the time of death could not be ascertained (Table 9).

TABLE 8
CAUSE OF DEATH IN PATIENTS KNOWN TO BE DEAD

	Cases.
Unknown, without knowledge of the presence of recurrence.....	23
With known recurrences.....	104
From disease other than cancer*.....	11†
Pneumonia.....	1
Grippe.....	1
Pernicious anemia.....	1
Apoplexy.....	1
Bright's disease.....	1
Cholecystitis.....	1
Gangrene of both legs (thrombosis?).....	1
Heart disease.....	4
	138

* In four cases letters definitely stated that there were no recurrences to the date of death. In seven cases no mention of a recurrence was made in replies received.

† The ages of these eleven patients were 46, 47, 50, 55, 56, 59, 64, 64, 64, 67, and 73.

TABLE 9
DURATION OF LIFE IN PATIENTS WHO ARE KNOWN TO BE DEAD‡

Of the 218 patients operated on	6 (2.7 per cent) died within 6 months after operation
	46 (21.1 per cent) died within 1 year after operation
	76 (34.9 per cent) died within 2 years after operation
	92 (42.2 per cent) died within 3 years after operation
	107 (49.1 per cent) died within 4 years after operation
	120 (55.0 per cent) died within 5 years after operation
	5 (2.3 per cent) died after 5 years
Of the 138 patients who died	6 (4.3 per cent) died within 6 months after operation
	46 (33.3 per cent) died within 1 year after operation
	76 (55.0 per cent) died within 2 years after operation
	92 (66.7 per cent) died within 3 years after operation
	107 (77.5 per cent) died within 4 years after operation
	120 (87.0 per cent) died within 5 years after operation
	5 (3.6 per cent) died after 5 years

‡ In thirteen the time of death following operation was unknown.

THREE-YEAR CURES

It is generally conceded that freedom from recurrence for three years does not constitute a cure. Five years' freedom from recurrence offers a much better chance for cure. In the series of 218 patients only

2.3 per cent died after five years. It was found that at the end of three years forty-eight (36.6 per cent) of the 132 patients whose glands were involved at the time of operation were alive, and that sixty-five (75.6 per cent) of the eighty-six patients without glandular involvement at the time of operation were alive. Regardless of glandular involvement, 113 (51.8 per cent) of the 218 patients were alive at the end of three years. Some of these patients had recurrences at this time and died later.

FIVE-YEAR CURES

At the end of five years twenty-nine (22 per cent) of the 132 patients in whom glandular involvement was demonstrated at the time of operation were alive, and fifty-six (65.1 per cent) of the eighty-six patients in whom the glands were not involved at the time of operation were alive. Regardless of glandular involvement of the 218 patients eighty-five (39 per cent) were alive at the end of five years (Table 10).

TABLE 10
THREE-, FIVE-, AND EIGHT-YEAR CURES*

Decade.		Cases.	Alive three years after operation.	Alive five years after operation.	Alive five to eight years after operation
20 to 30	With glandular involvement. . .	3	0	0	0
	Without glandular involvement.	1	1	1	1
30 to 40	With glandular involvement. . .	16	4	1	1
	Without glandular involvement.	15	11	9	9
40 to 50	With glandular involvement. . . .	50	17	10	8
	Without glandular involvement.	25	20	16	16
50 to 60	With glandular involvement. . .	28	10	8	8
	Without glandular involvement.	31	24	22	22
60 to 70	With glandular involvement. . .	26	12	8	6
	Without glandular involvement.	11	7	6	5
70 to 80	With glandular involvement. . .	9	5	2	2
	Without glandular involvement.	3	2	2	2
		218	113 (51.8%)	85 (39 %)	80 (36.7%)
Total with glandular involvement. . .		132	48 (36.6%)	29 (21.9%)	25 (18.9%)
Total without glandular involvement. .		86	65 (75.6%)	56 (65.1%)	55 (63.9%)

* In thirteen cases the exact date of death was unknown.

SIMPLE AMPUTATIONS OF THE BREAST FOR CARCINOMA

Simple amputations of the breast were performed for supposed mastitis in six cases; the condition was later reported by the pathologist as early cancer. Five of the six patients were traced. One is alive eight years after operation, two are alive seven years, and one is alive six years. One died four years after operation, but we were unable to ascertain the cause of death. The sixth patient was alive and without recurrence when last heard from, two years after operation. These six patients are not included in the series of 218 because radical amputations were not performed. The group, however, shows the excellent result which may be obtained when even incomplete operations are performed during the early stages of the disease; four (66.7 per cent) of the group are known to be alive and without recurrence for from six to eight years after operation, with a possibility that one more of the group is alive.

REMOVAL OF THE TUMOR FOR DIAGNOSIS BEFORE THE RADICAL AMPUTATION

In five patients in the series the original tumor had been removed for diagnosis from two days to two months before operation, and in one patient an abscess had been drained and a specimen removed for diagnosis eleven days before the radical amputation. Four of these patients (66.7 per cent) are known to be alive from five to eight years after operation. In four the tumor was removed for microscopic diagnosis and a radical amputation was performed immediately. Three of these patients (75 per cent) are living and without recurrence from five to eight years after operation. The other patient is dead. The carcinoma in this instance, however, was of the diffuse type and was cut into during the removal of the tumor for diagnosis. The prognosis in cases in which the tumor is first widely removed for diagnosis is not necessarily worse than when a primary radical amputation is performed.

THE MANAGEMENT OF TEETH DURING PREGNANCY*

WALTER N. ROWLEY

Mention of toothache and dental caries during pregnancy is found in all text books and in most articles on prenatal care. The statements that these patients should be "referred to a competent dentist" and "proper dental care instituted" are often seen, but there is little further in the way of comment or instruction.

Ballantyne, in a study of 100 cases in the Edinburgh Royal Maternity Hospital Antenatal Clinic, noted that 98 per cent of pregnant patients had dental caries or infection, and 93 per cent had submitted to one or more extractions. Fifty-three per cent of the patients were less than twenty-five years of age and only two of these had undecayed teeth. The histories of these patients showed that the most common dental procedure was wholesale extraction and the use of plates; 48 per cent of the 100 patients wore one or more plates. In a few instances a history of dental manipulation during pregnancy was elicited, but generally there was a prejudice against such interference during the expectant period and carious teeth were left strictly alone. Ballantyne believes that carious and infected teeth cannot fail to react on the mother's condition and retard the return to complete health in the puerperium. He argues that if surgical operations within the abdomen can be safely carried out during pregnancy, dental work can be done at this time. Goodman advises the early care of dental conditions in these patients and mentions the fact that dentists still fear the danger of abortion resulting from dental manipulation. He quotes Waller's experience which led him to believe that if the removal of dental foci is adequately carried out, even after it has produced symptoms, improvement in the mother's health is sufficiently rapid and substantial to be of signal benefit to the child. Roentgen-ray examination is a necessary preliminary to the removal of the infected teeth.

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La Vake mentions infected teeth and tonsils as a possible cause of nephritis in pregnancy, of preëclamptic toxemia, and of eclampsia; he reviews thirteen cases in which infection was a prominent feature. All his patients either had preclamptic toxemia or eclampsia, and all gave histories of endocarditis, rheumatism, toothache, and oral or tonsillar infection. Fever was present in all cases before convulsions occurred or before manipulation. Six of the patients were multiparas whose labors previously had been normal and who had a history of infection since the first pregnancy.

La Vake believes that every pregnant patient should be given a thorough dental examination with immediate eradication of foci of infection. He has never observed a case of abortion which could be attributed to dental manipulation. De Lee states that during pregnancy the teeth decay more easily than otherwise, due to alteration of the secretions of the mouth, perhaps because of the demand of the fetus for more calcium salts, or because the teeth partake of the general changes exhibited by the osseous system. He also considers it possible that certain obscure puerperal infections have their origin in abscessed teeth. The authors of most texts on obstetrics mention the superstition of the laity and the mistaken idea current among members of the dental profession with regard to the dangers that might result from dental extraction; no particular information is given further than that extractions may be done under gas and that extensive fillings should not be attempted.

Because the burden of conducting a woman through pregnancy to ultimate good health with the added comfort of a healthy child falls on the obstetrician, more and more coöperation is necessary in order that the best advice and care may be given to the mother. Focal infection with its possible effect has been a subject discussed with lively interest by the medical and dental professions for the past few years, and the teeth have become recognized as a vital factor.

Full mouth roentgenograms are made in the Mayo Clinic of every pregnant patient presenting any signs of dental or oral disease. Furthermore, a careful interpretation of these findings is made with the basic condition primarily in mind, and treatment is advised with a view to preserving the maximum usefulness of the remaining teeth, should extraction be carried out. Whenever a diagnosis of periapical infection is made, extraction is usually advised. If caries is advanced to such a degree that devitalization is necessary for proper restorative

dentistry, extraction is preferred, since tiring dental manipulation is believed to be detrimental to the health of the patient, and experience has shown that many devitalized teeth develop periapical infection. During pregnancy temporary cement fillings for cavities in vital teeth are preferred to more permanent inlays, and so forth. Cultures from roots of devitalized teeth extracted in the dental section of the Mayo Clinic have consistently shown a positive growth of streptococci, usually the viridans type.⁴ Pyorrhea should be treated by conservative measures and prophylaxis instituted when indicated.

In determining which of several periapically infected teeth should be extracted the general condition of the patient is considered, signs of trouble attributable to focal infection are sought, and other sources eliminated as far as possible. Extraction may be advised in the presence of periapical infection, even though symptoms attributable to foci of infection are wanting. Teeth with frank involvement of the surrounding bony structure are selected first. Examination of the urine is always made at each antenatal visit, and if the patient is sent for the extraction of one or more selected teeth, later urinalyses are made. The local, as well as the general, reaction is carefully noted and taken into consideration before further extractions. Practically no general reaction is noted, even in cases of marked osseous involvement. In cases in which a slight general reaction is anticipated, temperature readings are made, but a rise is not often noted. When a slight general reaction is manifested following the first extraction more time is allowed between operations. The patients rarely show reaction after the second extraction, possibly as a result of immunization following the first extraction. Leukocyte counts are made in some instances; a group of cases is now being studied in which differential blood counts are made before and after extraction. A slight rise in the leukocyte count has been noted in a few cases. Most of the extractions are done by surgical technic, as described by Novitsky, Shearer, and Gardner. The granuloma is removed intact; the amount of trauma is minimized, and absorption is reduced. This accounts at least in part for the absence of general reaction.

A small group of thirty patients, reviewed preliminary to further work on dental management, shows a diversified type of case, represents nearly all periods of pregnancy, and includes instances of single extractions as well as extensive removal of infection from the mouth. In not a few cases there were complications to pregnancy, and removal

of dental foci was only part of the general treatment. Twenty-two of the patients were more than twenty-five years of age, fifteen were in their first pregnancy, eight in their second, three in their third, two in their fourth, and two in their fifth. One of these had had nine gestations and only one full-term child.

The number of teeth extracted varies from eight cases, with one extraction each, to one case with fifteen extractions.

The period of gestation during which the extraction was done varied with the time the patient first presented herself for examination and with her condition. Eleven had extractions in the first trimester; this includes patients suffering with nausea and vomiting. Many patients did not present themselves for examination until the seventh month of pregnancy, and at this time seven patients had extractions. Six patients were examined soon after they felt quickening. Eight patients had extractions between the fourth and the fifth month, two in the sixth month, and two in the ninth month. Twenty were delivered at term; four are still pregnant and under observation; two aborted; four went into labor prematurely, one spontaneously, in the others labor was induced because of complications.

In the two cases of abortion the miscarriages were not dependent on the dental manipulation.

Case 1 (A233969). Mrs. F., primipara, aged twenty-four years, came for examination because of nausea and vomiting at the seventh week. The uterus was anteфлекed. One tooth was extracted by her husband, a dentist. In seven days nausea and vomiting subsided so she was comfortable throughout the day. Six weeks later, about twelve hours after driving several hours over frozen roads, pain and bleeding commenced; abortion occurred two days later.

Case 2 (A360904). Mrs. S., primipara, aged eighteen years, suffered from marked nausea and vomiting. The uterus was acutely anteфлекed. Three abscessed teeth were removed in the second month of pregnancy. Seven days later the patient left the hospital relieved of the nausea and vomiting. At four and one-half months abortion occurred at home. Her home physician attended her and no cause was given; but it is likely the anteфлекion and farm work which she did were the most probable causes.

Labor was induced prematurely in four cases; in three of these because of marked albuminuria with evidence of renal damage in the eighth month. The babies and mothers survived without incident. In one case labor was induced at the sixth month for severe neuroretinitis. Another patient had a normal full-term pregnancy and then had seven abortions in the third or fourth months. During the ninth pregnancy her general condition improved very much after tonsillectomy and the extraction of seven teeth. The blood pressure dropped from 170 systolic to 130 systolic, and from 126 diastolic to 90 diastolic. Pregnancy carried to seven months or a little over. An acute "cold" of moderate severity was followed by a sudden rise of blood pressure from 130 systolic to 180 systolic. Fetal movements stopped. Labor was induced and the patient delivered a

still-born child with multiple recent hemorrhages of the skin, liver, brain, and lungs. The fourth patient left the Clinic and was not heard from until two months later, when labor started prematurely at the seventh month, nearly three months after her extractions had been done.

The most interesting case from the standpoint of benefit from extraction of abscessed teeth is that of a woman who presented herself for examination at the seventh month of pregnancy because of dyspnea, exhaustion, and rheumatic pains in nearly every joint. General examination led to the diagnosis of mitral endocarditis with insufficiency, aortic endocarditis with insufficiency, chronic rheumatic arthritis, and marked oral and dental sepsis. The upper left gum was markedly swollen; purulent material could be expressed from many points; and most of the teeth were carious and destroyed to the gum margin. The blood pressure was 140 systolic and 75 diastolic; the pulse rate was 120 per minute. The urine showed a trace of albumin. The temperature was normal and a blood culture was negative after forty-eight hours on a blood-agar slant. The left side of the upper jaw was cleaned up at the first operation and no change of the urine, temperature, and blood culture followed. The remaining teeth and roots were later removed, sixteen in all. Improvement was marked in ten days, and she returned for delivery one month later, when examination revealed the blood pressure to be 122 systolic, 76 diastolic, and pulse rate 84 per minute. There was no dyspnea, except on exertion; the pulse was more regular, the heart was reduced in size, and compensation was restored. Two months postpartum the tonsils were removed and dental work completed for full plates.

The study of this group of cases has led me to believe that the removal of teeth with periapical infection and extensive caries can be safely done during pregnancy. Surgical removal in such cases is preferable in the presence of definite roentgenologic evidence of granuloma. Careful roentgen-ray examination, interpretation, and coöperation with the dentist are highly essential. Surgical extractions in these cases should be done according to a definite plan, with a careful consideration of the number of teeth to be removed at one operation, the condition of the patient, and her reaction following the first extraction. Repeated examination of the urine, temperature, and leukocytes should be made, and the general symptoms of reaction manifested by the patient should be carefully observed. Pyorrhea should not be overlooked and cavities in vital teeth should be filled with cement rather than with more permanent materials. In the presence of pathologic conditions associated with pregnancy the same precautions must be taken as are observed in similar conditions existing independently of pregnancy. The eradication of foci of infection other than the teeth is equally important in the hygiene of pregnancy.

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THE TREATMENT OF PRIMARY CARCINOMA OF THE VAGINA WITH RADIUM*

LEDA J. STACY

I am presenting this paper for the purpose of calling the attention of radiologists to the treatment by radium of primary carcinoma of the vagina, and with the hope of stimulating more frequent reports of cases giving the methods of treatment and the ultimate results obtained. I have found only three cases reported in the American literature.

Ward, in 1908, reported a case in which the disease had extended to the rectum and a rectovaginal fistula had formed two months after the application of the radium. Levin and Griffith both reported cases in 1914; reports were made three months after the completion of the treatment and both local and general improvement was marked.

Primary carcinoma of the vagina is comparatively rare. Williams states that less than 1 per cent of all cancers in women are of vaginal origin. The lesion usually occurs between the ages of thirty and forty years. Williams reported the case of the youngest patient on record, a girl of seventeen years. He believes that the often quoted cases of Guersant and of Johannovsky in which the patients were three and one-half years and nine years respectively, were of sarcoma and not carcinoma. In our series of twenty-one cases the youngest patient was twenty-eight years. Three patients (14.28 per cent) were under thirty-five, the average age was fifty and fourteen-hundredths years.

Apparently trauma is not an etiologic factor in these cases, for otherwise carcinoma would occur more frequently, since the vagina is subjected to many injuries from childbirth, prolapsus uteri, and the use of pessaries. Seventy-six and nineteen-hundredths per cent of our patients had had children. None of them had prolapse of the uterus.

All observers report that the growth occurs most frequently in the upper posterior portion of the vagina. In our series 42.8 per cent

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occurred on the posterior surface; 28.5 per cent on the anterior, and in 23.7 per cent there was involvement of most of the vaginal mucous membrane.

The course of the disease is very rapid. The average length of life following the first symptoms has been estimated sixteen and one-half months, the longest twenty-five to twenty-six months and the shortest eight months. The rapid course and early glandular involvement are due to the free lymphatic supply of the vaginal mucous membrane.

Three groups of lymphatics drain into the pelvic glands from the vagina. A superior group arises from the upper third of the vagina and passes in front of the ureter, is joined by vessels from the cervix, and empties in the middle chain of the external iliac glands. The middle group comes from the middle third of the vagina and terminates in the hypogastric gland situated at the origin of the vaginal artery. The inferior group drains the lower third of the rectovaginal septum, travels along between the rectum and the sacro-recto-genital aponeurosis, and terminates in the gland of the promontory of the sacrum. The lymphatics of the vagina anastomose with those from the cervix, the vulva, and the rectum (Poirier, Cunéo, and Delamere). This lymphatic supply explains the disappointing results in the surgical treatment of cancer in this location and also the subsequent glandular involvement when the local growth has been cured by radium. Metastasis to distant organs, however, is rare.

The symptoms of carcinoma of the vagina do not differ from those of carcinoma of the cervix. In our cases bloody discharge, leukorrhea, and in 52.63 per cent malodorous discharge were noted. Pain is not an early symptom and occurred in only 57.14 per cent. It is described usually as a low backache, or as inguinal.

Of the twenty-one patients with primary carcinoma of the vagina treated at the Mayo Clinic from July, 1915 to January, 1921 information concerning fourteen has been obtained recently in answer to questionnaires. Seven of the fourteen are living. One has lived three years and nine months, one two years and nine months, one two years and one month, one one year and two months, two six months, and one five months. Of those who died, one died two years and four months after treatment, one died one year and three months after treatment, one died one year after treatment, two died eleven months after treatment, and two died seven months after treatment.

SUMMARY OF THE CASE HISTORIES OF THE SEVEN PATIENTS WHO ARE
LIVING

Case 1 (A189193). Mrs. J. A., aged fifty-eight years, had passed the menopause eight years before. For two years she had had a watery irritating vaginal discharge, recently tinged with blood, some pelvic discomfort and bearing-down pain. A small papular roughness of vaginal mucous membrane, on the left anterior wall of the vagina just within the introitus, was slightly indurated and bleeding. No glands were palpable. Fifty milligrams of radium salt were given for six hours directly against the ulcerated area. A specimen of the lesion removed one month later was reported to be inflammatory. The patient reported three years and nine months after treatment. She had recently lost 35 pounds in weight, but had no pelvic pain nor vaginal discharge.

Case 2 (A226588). Mrs. H. G. F., aged eighty years. Three months before, the patient had noticed a growth in the posterior vulva and occasional bleeding. A cauliflower growth, superficial, with very little induration, involved the posterior vaginal orifice and extended on to the perineum. The inguinal glands were not palpable. Two applications were made of the 25 mg. plaque for fourteen hours each with 2 mm. brass and one-half inch gauze screening, and 2,000 mg. hours over the inguinal glands. Two months later 50 mg. radium salt were given for ten hours and twenty hours respectively over the posterior vulva and perineum. The patient reported two years and nine months later. Her general health was good, and there was no evidence of local trouble and no discharge.

Case 3 (A257542). Mrs. J. J. B., aged fifty years, menstruated irregularly, and had had pain in the back and hips, and occasionally intermenstrual bleeding for two or three months. She had lost slightly in weight. The posterior vaginal wall was indurated, nodular, and with some ulceration extending to within one-half inch of the introitus. The cervix was atrophied. No glands were palpated. Four vaginal treatments of 50 mg. hours of radium salt for fourteen hours, screening with one-half inch gauze and 2 mm. brass, and posteriorly by 2 mm. lead, and two rectal applications of 50 mg. hours for two hours, at intervals of from three to four days were given. Roentgen-ray exposures were made over the abdomen and back. The patient returned two months later. She had gained in weight and strength, and was free from pain and discharge. Examination showed two indurated and nodular areas, one in the posterior vault of the vagina and one just within the introitus. There was no evidence of glandular involvement. Two applications of radium to the vagina, two to the rectum, and roentgen-ray treatment were given. The patient returned five months later still in good health and free from discharge. The vaginal mucous membrane was smooth, with slight induration in the anterior vaginal wall. The left inguinal gland was 2 by 1.5 cm. Another course of treatment was given as before, and also radium exposure over the inguinal glands. The patient was last seen August, 1920. She complained of pain in the back and hips and down the right leg, and recently occasional slight amounts of dark blood passed by rectum; defecation was not painful. She had the same clear odorless vaginal discharge; she had not lost weight. The vaginal mucous membrane was smooth, the vagina slightly contracted. The left inguinal glands were enlarged and a few small glands were palpable by rectal examination. The rectal mucous membrane was smooth. The patient was given one vaginal treatment of 700 mg. hours (50 mg. radium salt for fourteen hours) and 2,752 mg. hours over the left inguinal region. Two years and one month after the first examination the patient reported a poor general condition.

Case 4 (A304826). Mrs. W. M. S., aged sixty-two years, had passed the menopause ten years before. For five months she had had a slight blood-streaked vaginal discharge.

recently with a slight odor. She had lost but little in weight. An indurated nodular growth was found involving the vault of the vagina. Three cervical applications of 50 mg. radium salt for fourteen hours were given, one vaginal application of 68 mg. for ten hours, and two rectal applications of 100 mg. hours each. Three months later three vaginal treatments of 700 mg. hours each and two rectal treatments of 200 mg. hours each were given. Six months later two vaginal treatments of 700 mg. hours each were given. The patient returned in six months, one year and two months after the first treatment, reporting a gain in weight and in strength, and practically no discharge. She was doing her own housework. The vaginal mucous membrane was found to be thickened and there was a small soft nodule on the posterior wall of the vagina. The vagina was shortened and the cervix flush with the vault. The left broad ligament was slightly thickened. A proctoscopic examination showed a slight ulcerated area on the anterior rectal wall. The patient was given roentgen-ray treatment to the abdomen and back, but no more radium treatment.

Case 5 (A337534). Mrs. C. E. R., aged thirty-six years, had menstruated regularly. For four months she had noted an occasional bloody discharge and pain in the vagina radiating into the back. Her general health was good. An epithelioma 5 cm. in diameter was found on the posterior wall of the vagina. The cervix was free from involvement. No glands were palpable and the rectal examination was negative. The pathologist reported epithelioma Grade 3. Five exposures of 50 mg. radium salt for fourteen hours each, at from three- to five-day intervals, and roentgen-ray treatment over the abdomen and back were given. The patient returned six months later. She had gained in weight, had very slight, if any, vaginal discharge, and no pain. She had had two menstrual periods since treatment. The vaginal mucous membrane was smooth and not indurated; the cervix was free from involvement, and the uterus movable. Examination of the rectum was negative. The patient was given roentgen-ray treatments over the abdomen and back, but no further radium. She was advised to report in four months.

Case 6 (A324912). Mrs. A. F. C., aged sixty-nine years, had passed the menopause twenty-two years before. For three months she had had a bloody vaginal discharge, and had lost slightly in weight. On the posterior wall of the vagina was a proliferating tumor about 2.5 cm. long. No glands were palpable. The pathologist reported epithelioma, Grade 4. Three vaginal exposures of 50 mg. for fourteen hours, and roentgen ray over the abdomen and back were given. A physician who examined her recently found no evidence of malignancy and reported her general health good six months after the treatment.

Case 7 (A338979). Mrs. C. R. S., aged sixty-three years, had passed the menopause seven years before. For six weeks she had noticed mucous vaginal discharge, but no bleeding. A proliferating growth 2 to 3 cm. in diameter was found on the posterior wall of the vagina; it was superficial, and no glands were palpable. The pathologist reported squamous-cell epithelioma, Grade 3. The patient was given one application of 50 mg. radium salt for fourteen hours in a wax mold, and two days later emanation needles were buried to approximate 518 mg. hours. Four days later the growth was excised with a portion of the posterior vaginal wall. Twelve days later two more treatments of 50 mg. for fourteen hours were applied. The patient was recently examined five months after the first treatment by a physician who reported the local and general condition to be good.

SUMMARY OF THE CASE HISTORIES OF THE SEVEN PATIENTS WHO

DIED

Case 8 (A250236). Mrs. M. O., aged forty-three years, had fallen astride a tub five months before, and since then had bled irregularly and had noticed a mass in the vagina. Examination revealed a cauliflower growth involving the anterior wall of the right vaginal wall. The uterus was movable. A total of 1,750 mg. hours of radium salt was given into the vagina in three treatments, and two rectal treatments of 100 mg. hours each were given. The patient returned three months later stating that all discharge had ceased two weeks after the treatment, but a small new growth had appeared just above the vulva. Two vaginal treatments of 700 mg. hours each were given. When she returned one month later the vaginal mucous membrane was smooth and there were no adhesions. No induration was detected by rectal examination. Two months later there was a small ulcerated area on the anterior vaginal wall and this was exposed to 600 mg. hours of radium salt. The patient was not seen again until one year and three months after the first examination and eight months after the last radium treatment. There was no evidence of malignancy at this time and a diagnosis was made of a clinical cure. Six months later, however, she developed retroperitoneal tumors and died apparently of abdominal carcinoma, two years and four months after the first treatment.

Case 9 (A254632). Mrs. A. H. P., aged forty-one years, had had a pus-like discharge for seven months, and soreness around the vulva at intervals. Examination showed an ulcerating growth posterior to the urethra, about 3 cm. in size. She was given 600 mg. hours over the growth, and returned in two months. At this time there was an area of induration at the site of the growth, and induration of the labia, but the inguinal glands on both sides were enlarged. She was again given two treatments of 300 mg. hours each and roentgen-ray treatment over the glands. Three months later she returned for examination there was rather a deep ulceration, but it did not involve the urethra and the glands were still large and tender. Another series of 1,000 mg. hours of radium salt was given as before and roentgen-ray treatment. The patient died one year and three months after the first treatment.

Case 10 (A240391). Miss A. K., aged forty-four years, gave a history of intermittent bleeding for from seven to eight months, and examination showed a carcinoma involving nearly all of the vaginal mucous membrane, associated with thickening in the parametrial ligaments. She was given three series of 20,000 and 21,000 and 22,000 mg. hours of radium salt respectively at three months' intervals. There was local improvement but metastatic extension into the iliac glands, and the patient died one year after the first treatment.

Case 11 (A216384). Mrs. C. F., aged twenty-nine years, had a large prolapsed mass and ulcerating mass involving most of the posterior vaginal wall. This patient received 2,100 mg. hours by vagina (50 mg. for fourteen hours each for three applications) and 200 mg. hours by rectum. She improved after the first treatment, and three months later received a second series similar to the first. In two months and again in three months she had severe hemorrhages, and died eleven months after the first treatment.

Case 12 (A239851). Mrs. R. McT., aged fifty-eight years, gave a history of intermittent bleeding for one year. She had a polypoid mass 2.5 cm. long just within the entrance of the vagina, on the right and posterior surface, and nodules on both lateral walls. The inguinal glands were enlarged. She was given 1,200 mg. hours into the vagina. There was improvement following treatment was only temporary and she died eleven months after the first treatment.

Case 13 (A294093). Miss M. Van O., aged twenty-eight years, had had a profuse discharge from the vagina for five months and pain in that region for three months.

The entire lateral and posterior walls of the vagina were involved. The inguinal glands were not palpated. Three vaginal treatments of 700 mg. hours each and two rectal treatments 100 mg. hours each were given. The patient returned three months later. She had had three hemorrhages two weeks before. The entire mucous membrane of the vagina was nodular and bled easily. An examination by rectum revealed marked thickening in both broad ligaments. Another series of treatments was given consisting of 728 mg. hours into the cervix, 300 mg. hours into the rectum, and 1,400 mg. hours into the vagina. The patient died in three months, seven months after the first treatment.

Case 14 (A256510). Mrs. E. L., aged thirty-three years, had had a watery discharge from the vagina of foul odor for two months and pain for one month. Her menstrual periods had been regular. Examination revealed a large fungating growth on the left posterior surface of the vagina. The posterior lip of the cervix was granular, the inguinal glands were not palpated. Three vaginal treatments were given of 50 mg. radium salt for fourteen hours each and two rectal treatments of 50 mg. radium salt for two hours each. The patient died seven months later.

All the patients in this group were given roentgen-ray treatments over the abdomen and back in conjunction with the local radium applications, and as the technic of roentgen-ray treatment improves the results will improve, particularly in the recent cases in which the emanation needles are buried in the growth, or in which much larger doses of radium salt are given. The increasing efficiency of the roentgen-ray treatment is also an important factor. In our cases the local condition has been comparatively successfully controlled, but the extension into the glands has not been prevented. We have no doubt been overapprehensive of the development of vesicovaginal fistulas, and might have given heavier doses. Vesicovaginal fistulas and rectovaginal fistulas occurred in one case, one year after the beginning of the application of radium, following the third series of treatments.

SUMMARY

1. Primary carcinoma of the vagina is comparatively rare.
2. The symptoms are similar to those of carcinoma of the cervix.
3. The disease extends early to the iliac glands; it rarely extends to other organs.
4. Radium and roentgen-ray treatments offer better chances for a cure than surgery, and as the technic improves a larger number of permanent cures should be effected.
5. Better results are obtained and there is less danger of formation of fistula if the initial treatment by radium is heavy and not repeated, roentgen-ray exposures to abdomen and back being, however, continued.

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EPITHELIOMA OF THE GENITO-URINARY ORGANS*

ALBERT C. BRODERS

Malignant neoplasms of the genito-urinary organs that arise from protective epithelium vary from soft, frond-shaped papillary epitheliomas of the bladder and of the pelvis of the kidney to ulcerated indurated keratinized epitheliomas of the vulva and of the penis. The term "cancer" is used loosely, but it is very important to know type of cancer in a given case. No one would think of putting the viny garter snake and the death-dealing cobra in the same class, they are both snakes. No one would think of putting the basal epithelioma and the highly malignant melanotic epithelioma in same class, but they are both cancers. A neoplasm can accomplish what its cells can accomplish; if its cells are active, it is active. A neoplasm may be of papillary form, and of a low degree of malignancy, or it may be papillary and of a high degree of malignancy. It may be ulcerated and of a high degree of malignancy, or it may be flat ulcerated and of a low degree of malignancy.

In two previous articles on epithelioma I divided the lesions, from standpoint of cellular activity, into four groups. In grading epitheliomas one must always take into consideration the normal epithelium of the organ from which the epithelioma has arisen. The epithelium of the bladder, while of the protective type, differs from that of the lip and skin in that it lacks a well-defined keratinized or horny layer. Irritation in the bladder from a stone will produce an area of hyperkeratinization or leukoplakia for protective purposes just as the constant handling of an ax or shovel will produce areas of excessive keratinization on the palms of the hands in the form of calluses. Keratinization is a physiologic and not a pathologic process; without this

Presented before the Section on Pathology and Physiology at the Seventy-second Annual Session of the American Medical Association, Boston, June, 1921. This paper contains a complete tabulation of all data relating to epitheliomas of the genito-urinary organs as appears in the *Annals of Surgery*,

process we would not have hair, finger nails, and toe nails, and animals would not have hoofs and horns. The normal cervix has some keratinization, while a prolapsed uterus may have a rather marked keratinization of its cervix epidermis. The penis and labium have about the same amount of keratinization normally as the lip and skin.

Papillary epitheliomas of the bladder, microscopically, often resemble the normal folds of bladder epithelium. Often they are composed of slender cells which resemble those of the basal layer; they contain polyhedral cells resembling those of the upper layer. The grading of epitheliomas of the bladder depends on the proportion of these cells in the neoplasm compared with the spherical cells and irregular cells with prominent nucleoli (undifferentiated cells). Papillary epitheliomas of the pelvis of the kidney and ureter are similar in structure.

Epitheliomas of the cervix, vagina, labium, and penis can be graded on the basis of the proportion of keratinization and large flat squamous cells with small nuclei to the number of undifferentiated cells. Microscopically, some epitheliomas of the cervix and vagina resemble basal-cell epitheliomas of the skin; however, they should not be considered in the same group because they are highly malignant, and behave very much like the same type of epitheliomas of the tonsil and nasopharynx.

GRADES OF EPITHELIOMAS

I shall use the same grading of epitheliomas in this series of cases that I used in my two previous papers on epithelioma; that is, if about three-fourths of the epitheliomas are differentiated epithelium and one-fourth undifferentiated, they are graded 1 (Figs. 126, 127, and 128); if the differentiated and undifferentiated epithelium are about equal they are graded 2 (Figs. 129, 130, and 131); if the undifferentiated epithelium forms about three-fourths and the differentiated about one-fourth of the growth they are graded 3 (Figs. 132, 133, and 134); if there is no tendency to cell differentiation they are graded 4 (Figs. 135, 136, and 137). The number of mitotic figures and the number of cells with single large deeply staining nucleoli play an important part in the grading.

My primary object in presenting this paper is to furnish data that will have a practical bearing on prognosis. From this standpoint the size and location of the epithelioma are extremely important.



FIG. 127 (Case A83994).—Grade 1 epithelioma of the bladder.



FIG. 126 (Case A125824).—Grade 1 epithelioma of the penis.

process we would not have hair, finger nails, and toe nails, and animals would not have hoofs and horns. The normal cervix has some keratinization, while a prolapsed uterus may have a rather marked keratinization of its cervix epidermis. The penis and labium have about the same amount of keratinization normally as the lip and skin.

Papillary epitheliomas of the bladder, microscopically, often resemble the normal folds of bladder epithelium. Often they are composed of slender cells which resemble those of the basal layer; they contain polyhedral cells resembling those of the upper layer. The grading of epitheliomas of the bladder depends on the proportion of these cells in the neoplasm compared with the spherical cells and irregular cells with prominent nucleoli (undifferentiated cells). Papillary epitheliomas of the pelvis of the kidney and ureter are similar in structure.

Epitheliomas of the cervix, vagina, labium, and penis can be graded on the basis of the proportion of keratinization and large flat squamous cells with small nuclei to the number of undifferentiated cells. Microscopically, some epitheliomas of the cervix and vagina resemble basal-cell epitheliomas of the skin; however, they should not be considered in the same group because they are highly malignant. They behave very much like the same type of epitheliomas of the tonsil and nasopharynx.

GRADES OF EPITHELIOMAS

I shall use the same grading of epitheliomas in this series of cases that I used in my two previous papers on epithelioma; that is, if about three-fourths of the epitheliomas are differentiated epithelium and one-fourth undifferentiated, they are graded 1 (Figs. 126, 127, and 128); if the differentiated and undifferentiated epithelium are about equal they are graded 2 (Figs. 129, 130, and 131); if the undifferentiated epithelium forms about three-fourths and the differentiated about one-fourth of the growth they are graded 3 (Figs. 132, 133, and 134); if there is no tendency to cell differentiation they are graded 4 (Figs. 135, 136, and 137). The number of mitotic figures and the number of cells with single large deeply staining nucleoli play an important part in the grading.

My primary object in presenting this paper is to furnish data that will have a practical bearing on prognosis. From this standpoint the size and location of the epithelioma are extremely important.



FIG. 127 (Case A83984).—Grade 1 epithelioma of the bladder.

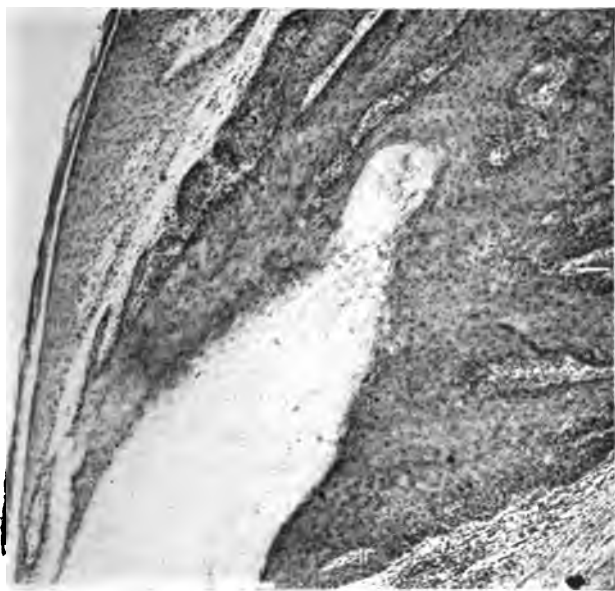


FIG. 126 (Case A125824).—Grade 1 epithelioma of the penis.



FIG. 129 (Case A72771).—Grade 2 epithelioma of the cervix.



FIG. 128 (Case A23702).—Grade 1 epithelioma of the bladder.

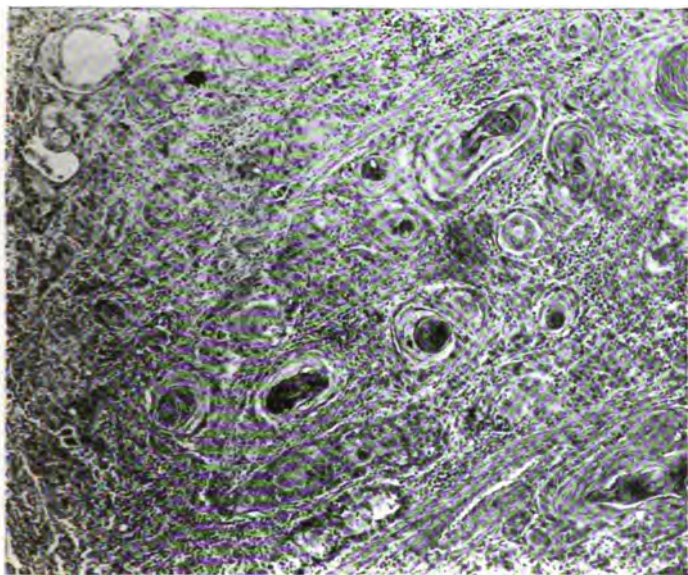


FIG. 131 (Case A115009).—Grade 2 epithelioma of the penis.

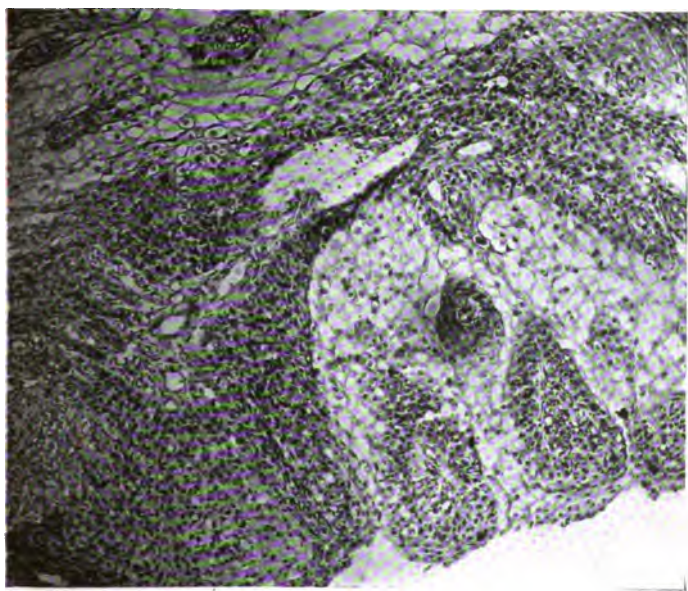


FIG. 130 (Case A27862).—Grade 2 epithelioma of the bladder.

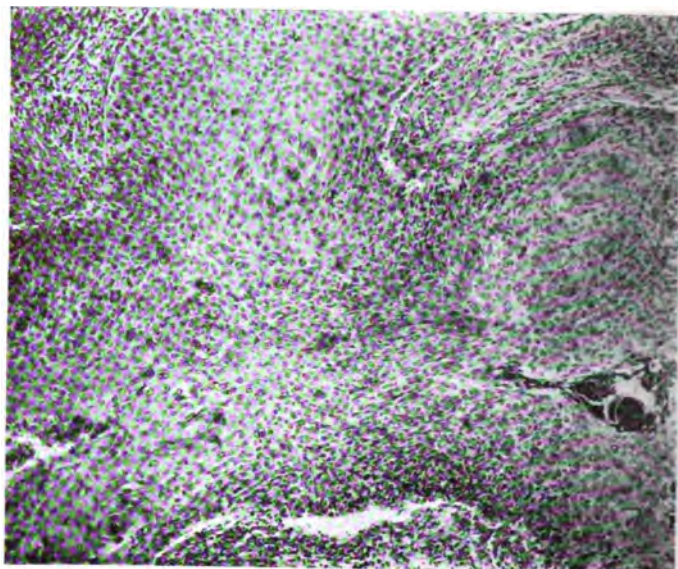


FIG. 199 (Case A90408).—Grade 3 epithelioma of the cervix.



FIG. 192 (Case A43008).—Grade 3 epithelioma of the cervix.

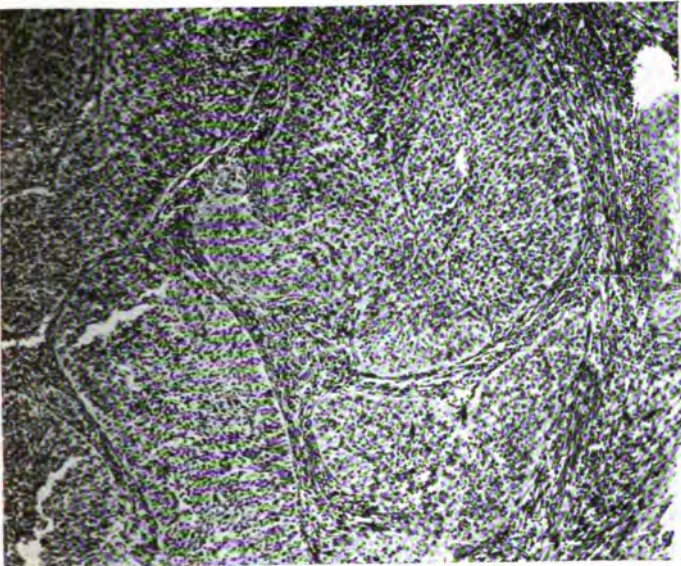


FIG. 135 (Case A89680).—Grade 4 epithelioma of the cervix.

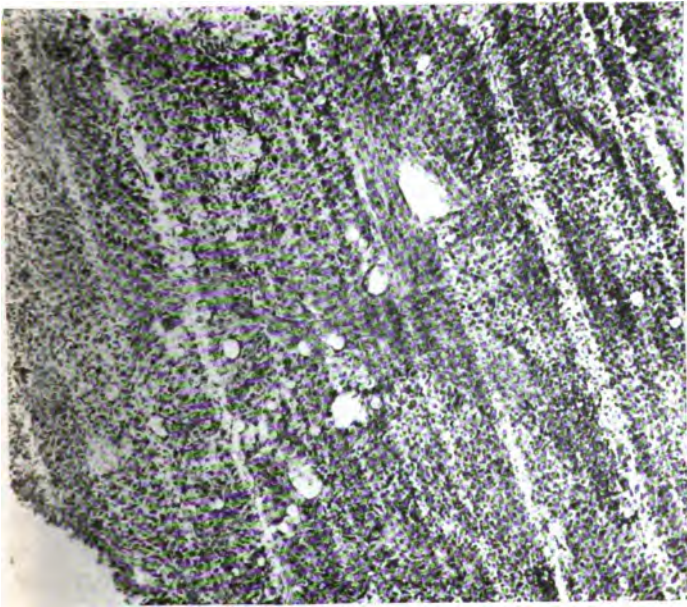


FIG. 134 (Case A30633).—Grade 3 epithelioma of the bladder.

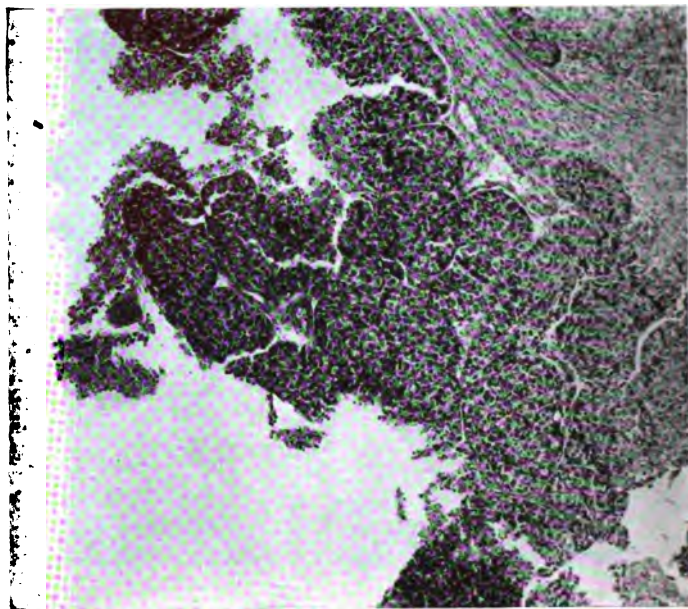


FIG. 187 (Case A88908).—Grade 4 epithelioma of the bladder.

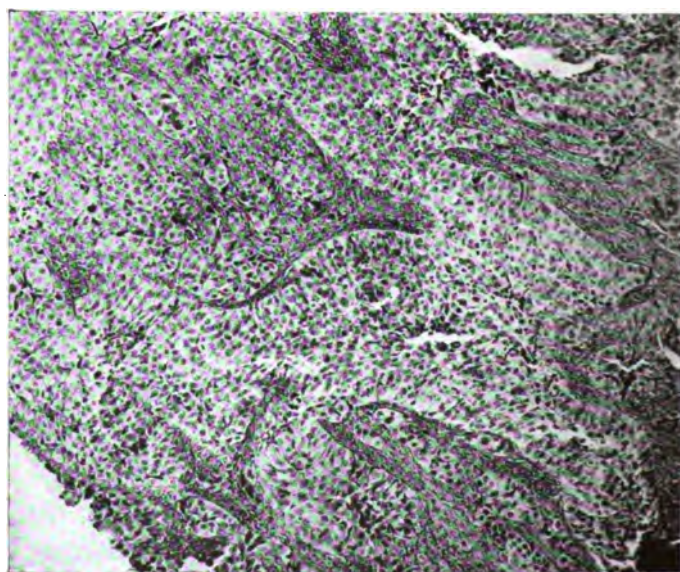


FIG. 188 (Case A81731).—Grade 4 epithelioma of the bladder.

Epithelioma may be relatively small and of an average degree of malignancy, but its location may make its complete extirpation, with the regional lymph nodes, almost impossible.

Exact dimensions of the lesion were obtained in most cases, but it is impossible to obtain them in all, especially if a cautery had been used; in these only approximate sizes were secured, which were divided, from the surgeon's description, into small, medium, and large. The cases in which the exact dimensions were obtained were also divided into three groups. If the greatest diameter of the lesion was 2 cm. or less it was considered small; if it was from 2 to 4 cm. it was considered medium, and if it was more than 4 cm. it was considered large. Thus, a combination of exact and approximate dimensions of practically all lesions were secured.

Metastasis was considered only when the lesion was in the labium or penis; it was not possible to obtain all the regional lymph nodes in other cases. Even in the cases of lesions in the labium or penis it was not possible to obtain all the regional lymph nodes because some of the lymphatics from these organs drain into the pelvis. In cases of lesions of other organs, especially the cervix and vagina, often only a small portion of the growth was obtained for examination, the remainder having been treated with the actual or the Percy cautery. In cases of lesions of the bladder lymph nodes were obtained only occasionally.

CONCLUSIONS

1. The 473 cases in this series represent 23.65 per cent of 2,000 cases of general epithelioma observed in the Mayo Clinic from November 1, 1914 to July 22, 1915.
2. Epithelioma of the genito-urinary organs occurred more often in females than in males; the proportion was about 3 to 1.
3. The average age of all patients was 50.04 years. The average age of patients with lesions of the cervix was 47.25 years, of the bladder 51 years, of the labium 57.87 years, of the penis 54.1 years, of the vagina 46.72 years, and of the urethra 57.75 years.
4. Ninety-five and ninety-eight hundredths per cent of all patients were married or had been married; 98.53 per cent of the patients with lesions of the cervix were married or had been married; 93.53 per cent of the patients with lesions of the labium were married or had been married; 93.08 per cent of the patients with lesions of the penis were married.

married or had been married; and 100 per cent of the patients with lesions of the vagina were married or had been married.

5. Thirty-three and eighty-five hundredths per cent of the men were farmers, in contrast to 56.7 per cent of farmers among the patients with squamous-cell epithelioma of the lip, and 53.96 per cent among patients with squamous-cell epithelioma of the skin.

6. Eleven and eighty-three hundredths per cent of the patients had a family history of malignancy.

7. Eighty-nine and thirty-four hundredths per cent of the patients with lesions of the cervix, 88.88 per cent with lesions of the labium, and 94.10 per cent with lesions of the vagina had been pregnant one or more times.

8. Forty-one and twenty-six hundredths per cent of the patients with lesions of the cervix had passed the menopause.

9. Ninety-three and sixty-three hundredths per cent of the patients with lesions of the cervix, 94.17 per cent with lesions of the bladder, 88.88 per cent with lesions of the vagina, and 75 per cent with lesions of the urethra gave histories of hemorrhage.

10. The average duration of the lesion in the cervix was 0.79 year, in the bladder 2.60 years, in the labium 1.73 years, in the penis 1.44 years, in the vagina 0.69 year, and in the urethra 0.87 year.

11. The average duration of the lesion in all of the patients was 1.35 years.

12. Sixty-six and thirty-nine hundredths per cent of the lesions of the cervix, 40.50 per cent of the bladder, 18.18 per cent of the labium, 22.73 per cent of the penis, and 71.42 per cent of the vagina were large.

13. Twenty-seven and twelve hundredths per cent of the lesions of the cervix, 51.89 per cent of the bladder, 50.09 per cent of the labium, 54.54 per cent of the penis, and 28.57 per cent of the vagina were medium.

14. Six and forty-seven hundredths per cent of the lesions of the cervix, 7.59 per cent of the bladder, 22.73 per cent of the labium, and 22.73 per cent of the penis were small.

15. Fifty-six and eighty-seven hundredths per cent of the epitheliomas of the genito-urinary organs were located in the cervix, 25.36 per cent in the bladder, 6.55 per cent on the labia, 6.13 per cent on the penis, 3.80 per cent in the vagina, 0.84 per cent in the urethra, 0.21 per cent in the pelvis of the kidney, and 0.21 per cent in the ovary.

16. Ninety-three and two hundredths per cent of all patients were operated on.

17. In 62.96 per cent of the operable cases of lesions of the labium the inguinal lymph nodes were removed; metastasis was demonstrated in 58.82 per cent.

18. In 78.57 per cent of operable lesions of the penis the inguinal lymph nodes were removed; metastasis was demonstrated in 18.18 per cent.

19. In a classification of the epitheliomas of all of the genito-urinary organs according to cellular activity, 5.07 per cent were graded 1, 24.52 per cent were graded 2, 43.55 per cent were graded 3, and 26.84 per cent were graded 4.

20. Seventy-six and fifty-nine hundredths per cent of the patients operated on have been traced; 21.36 per cent are living, 78.63 per cent are dead.

21. Ninety-four and forty-four hundredths per cent of the living patients report good results; they have lived on an average of 8.58 years since the last or only operation.

22. Excluding postoperative deaths and deaths in which the cause was not determined, 6.72 per cent of the patients obtained good results and lived on an average of 6.34 years after the last or only operation.

23. Excluding postoperative deaths and deaths in which the cause was not determined, 93.27 per cent of deaths were caused by epithelioma; these patients lived on an average of 1.84 years after the last or only operation.

24. Twenty and seventy-two hundredths per cent of patients with lesions of the cervix, who had been pregnant, obtained good results, and 79.26 per cent obtained poor results, contrasted with good results in 12.50 per cent and poor results in 87.50 per cent in those who had not been pregnant.

25. Ten and nine hundredths per cent of the patients with large lesions of the cervix obtained good results, and 89.90 per cent obtained poor results. Thirty-three and thirty-three hundredths per cent of patients with medium lesions obtained good results, and 66.66 per cent obtained poor results. One hundred per cent of patients with small lesions obtained good results.

26. Thirty-three and thirty-three hundredths per cent of patients with large lesions of the bladder obtained good results, and 66.66 per cent obtained poor results. Forty-six and sixty-six hundredths per

cent of patients with medium lesions of the bladder obtained good results, and 53.33 per cent poor results. Eighty per cent of the patients with small lesions of the bladder obtained good results and 20 per cent obtained poor results.

27. Nine and nine hundredths per cent of the patients with medium lesions of the labium obtained good results, and 90.90 per cent poor results. Twenty-five per cent of the patients with small lesions obtained good results, 25 per cent fair results, and 50 per cent poor results.

28. One hundred per cent of the patients with large lesions in the penis obtained poor results; 37.50 per cent of the patients with medium lesions obtained good results, 12.50 per cent fair results, and 50 per cent poor results; 66.66 per cent of the patients with small lesions obtained good results, and 33.33 per cent poor results.

29. One hundred per cent of the patients with large lesions in the vagina obtained poor results, and 100 per cent of the patients with medium lesions obtained good results.

30. Fourteen and twenty-eight hundredths per cent of the patients with metastasis who had lesions in the labium obtained good results, and 85.71 per cent poor results; 20 per cent of the patients without metastasis obtained good results, 20 per cent fair results, and 60 per cent poor results; 20 per cent of the patients in whom no regional lymph nodes were removed obtained good results, and 80 per cent poor results.

31. One hundred per cent of the patients with metastasis who had lesions in the penis obtained poor results, 63.63 per cent of the patients without metastasis obtained good results, 9.09 per cent fair results, 27.27 per cent poor results, and 100 per cent of the patients in whom no regional lymph nodes were removed obtained poor results.

32. Seventeen and seventy-seven hundredths per cent of the patients with lesions of the cervix are alive, with good results; they have been free from the disease for an average of 9.32 years.

33. Two and twenty-two hundredths per cent of the patients with lesions of the cervix obtained good results, and had been free from the disease an average of 6.05 years at the time of death.

34. Twenty per cent, or one in five, patients with lesions of the cervix obtained good results.

35. Eighty per cent of the patients with lesions of the cervix obtained poor results, and lived an average of 1.27 years.

36. Thirty-seven and fourteen hundredths per cent of the patients

with lesions of the bladder are alive, with good results; they have been free from the disease for an average of 7.54 years.

37. Eleven and forty-two hundredths per cent of the patients with lesions of the bladder obtained good results, and had been free from the disease an average of 6.26 years at the time of death.

38. Forty-eight and fifty-six hundredths per cent, nearly one-half of the patients, with lesions of the bladder obtained good results.

39. Two and eighty-five hundredths per cent of the patients with lesions of the bladder are alive, with fair results.

40. Forty-eight and fifty-seven hundredths per cent of the patients with lesions of the bladder obtained poor results; they lived for an average of 1.22 years.

41. Seventeen and sixty-four hundredths per cent of the patients with lesions of the labium are alive, with good results; they have been free from the disease for an average of 7.78 years.

42. Five and eighty-eight hundredths per cent of the patients, with lesions of the labium obtained fair results.

43. Seventy-six and forty-seven hundredths per cent of the patients with lesions of the labium obtained poor results; they lived an average of 2.47 years.

44. Twenty-three and fifty-two hundredths per cent of the patients with lesions of the penis are alive with good results; they have been free from the disease for an average of 10.42 years.

45. Seventeen and sixty-four hundredths per cent of the patients with lesions of the penis who are dead obtained good results and had been free from the disease an average of 6.95 years.

46. Forty-one and sixteen hundredths per cent of the patients with lesions of the penis obtained good results.

47. Five and eighty-eight hundredths per cent of the patients with lesions of the penis obtained fair results.

48. Fifty-two and ninety-four hundredths per cent of the patients with lesions of the penis who are dead obtained poor results; they lived for an average of 1.66 years.

49. Thirty-three and thirty-three hundredths per cent of the patients with lesions of the vagina are alive, with good results; they have been free from the disease for an average of 8.32 years.

50. Sixty-six and sixty-six hundredths per cent of the patients with lesions of the vagina obtained poor results and lived for an average of 0.61 year.

51. In a consideration of all the organs from the standpoint of the grade of malignancy relative to mortality and exclusive of deaths from unknown causes and deaths postoperatively, epithelioma was the cause of death in 83.33 per cent of patients in Grade 1, in 81.08 per cent in Grade 2, in 96.33 per cent in Grade 3, and 97.29 per cent in Grade 4.

52. The total good results for all organs were 83.33 per cent in Grade 1, 45.90 per cent in Grade 2, 25 per cent in Grade 3, and 12.19 per cent in Grade 4.

53. The total poor results for all organs were 8.33 per cent in Grade 1, 49.18 per cent in Grade 2, 75 per cent in Grade 3, and 87.80 per cent in Grade 4.

54. Twenty-three and five hundredths per cent of all the patients are alive, with good results; they have been free from the disease for an average of 8.58 years; 5.08 per cent of the patients obtained good results and had been free from the disease for an average of 6.34 years at the time of death; 28.13 per cent obtained good results; 1.35 per cent are alive, with fair results, and 70.50 per cent obtained poor results and lived for an average of 1.34 years.

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DUCTLESS GLANDS

THE INTERRELATIONSHIP OF THE FUNCTION OF THE THYROID GLAND AND OF ITS ACTIVE AGENT, THYROXIN, IN THE TISSUES OF THE BODY*

HENRY S. PLUMMER

The highly essential function of the thyroid is the elaboration and delivery to the body of thyroxin. The gland secretes and stores in its acini the so-called colloid. It seems highly probable that the latter function is an accessory to the production and storage of thyroxin, and that in it is stored iodine for the elaboration of this agent. There is no definite evidence that the thyroid has any other function.

THYROXIN

In 1914, Kendall separated from the thyroid gland the pure chemical compound thyroxin. He proved thyroxin to be its active agent. In 1915, in attempting to correlate the available data with regard to the function of the thyroid gland and of its active agent, thyroxin, in the tissues of the body, I formulated these deductions:

1. Thyroxin is active directly or indirectly in the cells throughout the tissues of the body.

2. Thyroxin is an agent hastening the rate of formation of a quantum of potential energy available for transformation on excitation of the cell.

3. Hyperthyroidism is the physiologic status of an individual otherwise normal when the thyroxin in the tissues is sufficient to hold the basal metabolism above normal.

4. Hypothyroidism is the opposite of hyperthyroidism.

5. All the phenomena in pure hyperthyroidism are those that must attend a sustained elevation of the basal metabolism.

6. The status of the hyperfunctioning adenomatous goiter is the result of a pure hyperthyroidism.

* Address of the Chairman of the Section on Practice of Medicine at the Seventy-second Annual Session of the American Medical Association, Boston, June, 1921. Reprinted from the Journal of the American Medical Association, 1921, lxxvii, 243-247.

7. The status of exophthalmic goiter is not accounted for by a pure hyperthyroidism.

Various observations correlated on these working hypotheses led me, in 1917, without previous estimates of the basal metabolism following the administration of thyroxin, to give intravenously to a myxedematous patient, supposedly having no thyroid gland, 22 mg. of thyroxin and to anticipate the reaction which followed. The reaction was approximately the average of those obtained from several hundred doses since administered. From these studies the following deductions may be drawn:

1. After the administration of a single dose of thyroxin sufficient to bring the basal metabolism to normal, the physiologic status of a thyroidless patient becomes normal in from ten to twelve days, remains approximately normal for ten days, and returns to the preëxisting status in from five to seven weeks.

2. The amount of thyroxin in the tissues (exclusive of the thyroid) of the average normal man is approximately 14 mg. Kendall, from an analysis of the iodine-content in the tissues, recently estimated the amount to be 14 mg.

3. The average daily exhaustion of thyroxin in the tissues is between 0.50 and 1 mg.

4. A shift of 1 mg. of thyroxin in the tissues of the body is accompanied by a corresponding rise or fall of between 2 and 3 per cent in the basal metabolism.

5. Fourteen milligrams of thyroxin given to a thyroidless person is not fully exhausted until from the end of the fifth to the eighth week.

Two milligrams of thyroxin a day may hold the basal metabolism from 20 to 30 per cent above normal; 3 mg. a day may hold the basal metabolism 50 per cent above normal.

Fifteen milligrams of thyroxin given intravenously to patients with exophthalmic goiter who have a basal metabolism above +65 may not cause notable reaction; when given to patients having large colloid goiter with bruit, the bruit disappears and the thyroid shrinks rapidly, but constitutional reaction may be absent. With these two exceptions a sustained elevation of the basal metabolism has followed every intravenous dose of more than 1 mg. of thyroxin.

The drop in the basal metabolism following the traumatic destruction of the entire thyroid, its resection for hyperfunctioning adenomatous goiter, the administration of a large dose of thyroxin or the withdrawal

of this agent after a period of daily administration is always gradual, extending over days. These observations indicate that the thyroid under average normal conditions maintains an approximately constant level of thyroxin in the body, and that an elevation of basal metabolism of more than 5 per cent followed within twenty-four hours by a corresponding drop cannot, except possibly in relatively high degrees of hyperthyroidism, be attributed to fluctuation in the thyroxin-content of the body.

Without knowing the exact mechanism of the normal stimulation of the thyroid we can assume that it is brought into play by a drop in the amount of thyroxin in the tissues of the body. This being true, the daily administration of 1 mg. or more of thyroxin should place the thyroid at partial or complete rest, at least so far as the production of this agent is concerned. Following this hypothesis, the daily administration of 0.5 to 1 mg. of thyroxin to a normal person might not be attended by any general physiologic reaction. We have given a daily dose of 1 mg. to a number of persons, apparently having a normal thyroid function, for months without any deflection of the basal metabolism from the normal. There are some objections to drawing definite conclusions from these results and from other observations which indicate that the thyroid gland is placed at rest by the administration of thyroxin; however, the mass of evidence supports the hypothesis.

There are approximately 10 mg. of thyroxin in 150 grains of desiccated thyroid. The physiologic reaction following the administration of thyroxin is, so far as we have made any observation, identical with that following the administration of the fresh or desiccated thyroid gland containing this agent. Absorption from the intestinal tract is, however, very erratic and desiccated thyroid cannot be given intravenously.

A daily oral dose of 1.6 mg. of thyroxin will hold the basal metabolism of most thyroidless individuals within the normal limits. In most instances the dose established two or three years ago has not had to be changed, the basal metabolism estimates being within 5 per cent of the average normal each time the patient has returned for observation. A daily dose of from 2 to 3 mg. of thyroxin or 20 grains of desiccated thyroid given by mouth will not fluctuate the basal metabolism or cause any physiologic reaction in many patients in whom this dose given intravenously causes the quantitative reaction almost standard for myxedematous patients. In isolated cases 250 grains of desiccated

thyroid has not caused any reaction. This failure of absorption or destruction of thyroxin before reaching the general circulation is characteristic of a considerable percentage of patients who have diffuse colloid goiter and of patients in the various groups having low basal metabolism readings not attributable to a primary hypothyroidism. This failure of absorption, the difficulty of carrying out daily intravenous administration over a long period, the probability that the thyroid is placed at partial or complete rest, and evidence that under certain conditions the thyroid picks up and stores part of the thyroxin, have been most baffling in the attempt to study quantitatively the reactions of persons having functioning thyroids.

As thyroxin, other factors remaining constant, determines the rate of transformation of energy in the organism, it can be assumed that the rate of exhaustion of thyroxin for a given period is determined, to a large extent at least, by the total transformation of energy. That the rate of exhaustion relative to the total metabolism is not the same in all the organs or reactions of the organism is probable. There is much to suggest that the rate of exhaustion of thyroxin in the female is higher than in the male.

It seems probable that the relation of the rate of exhaustion to the total metabolism for a given period might be roughly determined by fluctuating stress on a thyroidless person whose basal metabolism has been held at normal sufficiently long to permit of readjustment of physiologic functions. We have not, up to the present, been able to control such a patient for the required time.

It is quite probable that there is a gradual adaptation downward in the thyroxin-content of the tissues, and hence in the thyroid activity in some of the classifiable and unclassifiable conditions not primarily hypothyroid, with which a low basal metabolism is associated. The clearest evidence of this is the gradual adaptation downward of the basal metabolism to long continued low-food intake. The term secondary hypothyroidism might, though perhaps inadvisably, be applied to such a status. That a disuse-atrophy may result is possible if not probable. Assuming that the rate of exhaustion of thyroxin in the tissues should be determined largely by the total energy-transformation, and hence that disuse-atrophy and inability of the thyroid to respond to a suddenly increased demand might follow a prolonged low-food intake, three patients with hysterical dysphagia who had lived and worked hard on a very limited liquid diet for a number of years were

held under observation following the sudden relief of the dysphagia and return to a normal diet. As anticipated, the basal metabolism of each patient dropped from 10 to 22 per cent below normal in three weeks, and the edema, the skin changes, and other minor evidence of myxedema developed. This observation has added significance in the light of the following facts:

The basal metabolism of a thyroidless individual is from 30 to 40 per cent below the average normal. The edema of myxedema develops, or at least becomes recognizable, when the basal metabolism drops from 15 to 17 per cent below the average normal. In a myxedematous person having a basal metabolism ranging near this point the edema may appear after stress and disappear after rest. Sustained stress exhausts the thyroxin more rapidly than it can be produced by the thyroid and the basal metabolism drops a few points. A recognizable edema may disappear and reappear with a shift of 1 mg. or less of thyroxin in the tissues of the body. A drop in the basal metabolism to 40 per cent below normal does not cause edema in the classifiable and unclassifiable conditions not due primarily to hypothyroidism. This relation of edema to the basal metabolism is of the highest significance in the differential diagnosis of primary hypothyroidism and of the other conditions with which a low metabolism is associated.

If we are right in the inference that the amount of thyroxin in the tissues of the body throughout the range of normal or near-normal conditions is fairly constant, and that the rate of exhaustion is determined to a high degree by the total metabolism or fluctuations in specific metabolic reactions, the thyroid is subject to the greatest stimulation when the amount of this agent in the body is lowest, that is, when the tendency is toward hypothyroidism. This indicates that increased vascularity and histologic evidence of increased activity in the thyroid should not be accepted without hesitation as evidence of hyperthyroidization of the tissues of the body. This, of course, does not apply if the stimulus to the thyroid is not originating in the demands of the organism, as is probably true in pathologic conditions such as exophthalmic goiter and hyperfunctioning adenomatous goiter.

The ease with which the phenomena attending an elevation of the metabolism and an increased rate of exhaustion of thyroxin in the tissues from stimulation originating in the central nervous system and the resulting evidence of stress on the thyroid may be confused with the phenomena of hyperthyroidism is apparent when we recognize that

but for the transformation of part of the energy to motion, the phenomena of physical exertion and the resulting fatigue could be distinguished only with difficulty from those of pure hyperthyroidism. The phenomena of mild exophthalmic goiter are so much like the psychoneurotic manifestations due to lack of assurance that the thyroid is often resected for the latter condition. The lack of assurance is often cut out and both the physician and patient satisfied; the latter enjoys a period of ease after demanding restitution of fees from previous consultants.

THE THYROID GLAND

The normal thyroid gland is constituted of acini containing colloid and lined with relatively dormant appearing cuboidal or low columnar epithelium supported by the sustentacular tissue common to gland structure. Various interpretations have been placed on the groups of cells in the stroma of the gland; however, they are not known to have any definite specific function peculiar to the thyroid.

Three departures from this somewhat conventional picture of the normal thyroid gland dominate the study of the relationships of the anatomic changes and functional activity of the thyroid, and form the basis for the classification of conditions grouped under the term goiter: (1) hypertrophy of the alveolar epithelium; (2) an increase of the intra-alveolar colloid; and (3) the development of new alveoli. On these changes goiter may be primarily classified as hypertrophic, colloid, and adenomatous.

Diffuse colloid goiter and diffuse hypertrophic goiter may be considered anatomic expressions of functional disturbance in prenatally developed thyroid acini. Adenomatous goiter is new tissue developing postnatally from the stimulation of embryonic cells. All these types may be present in the same gland. Adenomatous tissue may be either encapsulated or nonencapsulated.

Three clear-cut abnormal physiologic states are associated with anatomic changes in the thyroid: (1) pure hyperthyroidism; (2) pure hypothyroidism; and (3) exophthalmic goiter.

A definite syndrome of hyperthyroidism is, with rare exceptions, associated with diffuse hypertrophic or adenomatous goiter, or follows the administration of thyroxin.

The assumption that the status of adenomatous goiter is attributable simply to an excess of the normal thyroid product (pure hyperthyroid-

ism) rests largely on a correlation of at least approximately accurate observations; they are as follows:

1. The physiologic status of a thyroidless individual returns to normal when the basal metabolism is brought to normal by the administration of thyroxin.

2. The phenomena induced by the administration of thyroxin and the phenomena associated with adenomatous goiter are identical and those that must attend a sustained elevation of the metabolism.

3. These phenomena disappear with the dropping of the basal metabolism to normal within three weeks after the enucleation of the adenoma.

The status of exophthalmic goiter, while in the main hyperthyroid, cannot be attributed wholly to an excess of the normal thyroid product. The characteristics of exophthalmic goiter may be due to an incomplete thyroxin molecule.

The capacity of the normal thyroid to elaborate thyroxin without notable histologic change is evidenced by the failure to demonstrate such changes after the resection of at least three-fourths of the thyroid. That the thyroid is subject to the laws of rest and repose; that it stores thyroxin, iodine and colloid, and that during periods of stress it absorbs a portion of the colloid, utilizes the stored iodine, and delivers thyroxin to the blood stream; that hypertrophy is indicative of a relatively high degree of stimulation; that intensive stimulation will cause hypertrophy and hyperfunction; and that the intracellular changes are indicative of the secretory processes of the thyroid vesicles functioning under normal conditions can be accepted with little, if any, reserve. However, several themes that pervade, if they do not dominate, the literature on the thyroid gland are open to question: (1) hypertrophy is indicative of the production of the active agent of the thyroid in excess of the average normal; (2) the storage of colloid in excess of the normal is indicative of a resting phase of the thyroid and is a result of damage from preëxisting hypertrophy and hyperplasia; and (3) the administration of iodine places the thyroid at rest.

For evident reasons we might anticipate that the administration of thyroxin to the point of supplying the demands of the organism would place the thyroid at rest and that the administration of iodine, if the supply of this element were otherwise deficient, would favor thyroid productivity.

Areas of hypertrophy, "some hypertrophy" (MacCarty), are present

in such a percentage of all thyroids resected that this degree of hypertrophy has little, if any, tangible significance. In exophthalmic goiter diffuse hypertrophy of the thyroid is rarely absent, but even in severe cases it varies from the most marked degree to the vanishing point. Diffuse hypertrophy unassociated with a syndrome that is or is not distinguishable from that of exophthalmic goiter is present in approximately only one or two of each 1,000 human thyroids resected. Many patients in this group later develop frank exophthalmic goiter. That all such thyroids are a part of this complex is possible if not probable. Whatever their significance, the incidence demonstrates that they have no relation to pregnancy, to adolescence, and to the conditions supposed to throw stress on the thyroid and produce diffuse hypertrophy. On the other hand, in each 1,000 thyroids resected for exophthalmic goiter in patients with a high basal metabolism and moderate exophthalmos, from one to three show only pure diffuse colloid goiter. I am confident that hypertrophy was present at the time the exophthalmos developed.

The thyroids of many domestic and wild animals become markedly hypertrophic with changes, such as of surroundings and diet, without any detectable constitutional disturbances. When hypertrophy is present the findings are often more readily attributable to causes throwing stress on the thyroid than to an excess of thyroxin in the tissues. This hypertrophy can be prevented or caused to disappear by the administration of iodine. The same is true of the hypertrophic goiter of fish (Gaylord). The goiters of pig cretins are hypertrophic, and the inference that they are under high stimulation is warranted. Iodine administered to the mothers prevents this type of goiter and the hypothyroidism, the immediate cause of the goiter, not the result.

The remnant of the thyroid of human cretins, if present, is usually distended with colloid. Diffuse hypertrophy is sometimes present. The nodules found in cretins usually shrink rapidly following the administration of thyroxin. Nodules 5 cm. in diameter may be reduced within three or four weeks to the point of being barely palpable. It has long been known that iodine favors the disappearance of colloid goiter. Marine has demonstrated that iodine administration prevents the development of diffuse colloid goiter in man. What may be considered the acme of diffuse colloid goiter is most prevalent from the seventeenth to the twenty-first year. Each lateral lobe may be as large as 8 or 10 cm. in diameter. The thyroid arteries are distended and

roll under the finger like a large lead pencil; bruit and loud thrill are present, and in the majority of cases the basal metabolism is from 8 to 15 per cent below the average normal. In from twelve to twenty-four hours following the administration of thyroxin the thyroid vessels are not palpable, and the bruit and thrill are no longer audible. The gland rapidly shrinks in size, in some instances becoming barely palpable in three weeks. The continuous administration of thyroxin prevents the reappearance of the goiter; however, on withdrawal of the drug the thyroid may rapidly attain its original size. After absorption of the colloid, iodine in many instances at least will prevent its redeposition. That colloid goiters are capable of producing thyroxin if sufficiently stimulated is demonstrated by the fact that the basal metabolism drops but little, if any, following a resection of the gland. The majority of diffuse colloid goiters that have come under our observation since we have fully recognized the fallacy in the absorption of thyroid preparations have been made to disappear or become barely palpable. The thyroid of the human cretin distended with colloid reacts as does the colloid goiter of adolescence. The preceding observations on the occurrence of colloid and hypertrophic goiter and their reactions to thyroxin and iodine administration can be correlated on the hypothesis which, if correct, is essential to our understanding of the relation of functional activity to anatomic changes in the thyroid. Without definite knowledge of the exact mechanism we can assume that the normal stimulation of the thyroid is brought into play by partial exhaustion of the thyroxin in the tissues. Factors interfering with the production of this agent lower the amount delivered from the thyroid. There may be several such factors. The one known factor is an actual or relative shortage of iodine. A thyroid so handicapped, if sufficiently stimulated, can produce a normal amount or even an excessive amount of thyroxin; however, relative to the normally functioning gland, it tends to lag behind the demands of the tissues, that is, it does not respond quantitatively to stimulation as does the normal thyroid. The degree of stimulation of such a gland is above the average and probably increases as the thyroxin content of the tissues drops. Basal metabolism estimations suggest that this lag expressed as the amount of thyroxin in the tissues never exceeds 4 mg. The human gland acting under these conditions deposits an excess of colloid in its acini. This constitutes the diffuse colloid goiter of adolescence. Diffuse colloid considered as an entity probably never hyperfunctions. That glands

of most animals acting under the same or similar conditions develop diffuse hypertrophy seems probable.

It might be contended that the deposit of colloid interferes with the function of the thyroid and thus causes a shortage of thyroxin in the tissues. The mass of data does not correlate with this theory as it does with the theory attributing the mild hypothyroidism and colloid deposit to a common factor, namely, stimulation of the thyroid acini which are in some way handicapped in their functional ability. A hypothyroidism of sufficient degree to cause edema is, according to our observations, never due to goiter.

ADENOMATOUS GOITERS

Goiters usually classified under the terms "simple," "endemic," "adolescent," and so forth, are diffuse colloid, adenomatous, or a combination, particularly at their inception, of the two types. The majority of such goiters are first noticed during the latter half of the second decade. The colloid goiter usually disappears before the twenty-fifth year; however, there is a tendency for a thyroid once overloaded with colloid, irrespective of its functional activity, to retain more than the normal amount, that is, sufficient to make the gland easily palpable throughout life. The adenomatous nodules, often during the early part of their history buried in colloid goiter, never disappear, although they fluctuate much in size with their colloid-content, vascularity, and degenerative changes.

The administration of iodine may prevent the formation of colloid goiter. That it may also be almost equally efficacious in the prevention of adenomatous goiter in adolescence seems probable. In fact, if the theme here presented is correct, to control adolescent goiter means to control adenomatous goiter also.

Two theories have prevailed with regard to hyperfunctioning adenomatous goiter: first, that the adenomatous tissue elaborates and delivers an excess of thyroxin, and second, that the adenoma in some way stimulates the surrounding thyroid tissue to hyperfunction. Though the question must still be considered open, the evidence correlates best with the theory that the adenomatous tissue hyperfunctions. Irrespective of the question of which type of tissue furnishes the excess of thyroxin, there is no doubt that the adenomatous tissue actually elaborates thyroxin and stores colloid and iodine. In the following discussion of adenomatous goiter the facts may be coordi-

nated with either theory; however, I have assumed that the adenoma hyperfunctions.

The majority of adenomatous goiters have their inception in colloid goiter. The embryonal cells seem to be stimulated through the same mechanism that forces the postnatally developed gland to maintain a normal level of thyroxin in the tissues. Possibly we should look on adenomatous tissue as a compensatory attempt. Such a theory does not eliminate the possibility that the formation of the new tissue may in some instances be excited by local irritants. Early in its life history new adenomatous tissue cannot function. A number of observations suggest that it can elaborate and store colloid long before it can elaborate and store thyroxin. It seems more prone, as does the prenatally developed thyroid tissues, to store colloid if it is unable to elaborate thyroxin or if the rate of stimulation of the thyroid is above the average normal. Only rarely are the factors such that the adenomatous tissue will function, at least to the point of causing hyperthyroidism, before the latter half of the third decade, although, as a rule, it is palpable in the second decade of life. The average interval between the time the adenomatous goiter is first noticed and the onset of hyperthyroidism, including only those that hyperfunction before coming under observation, is seventeen and one-half years. While the normal stimulating mechanism is a factor in the inception of the adenomatous goiter, once this tissue has started to function, it does so erratically and without relation to the needs of the individual. This observation is borne out by the fact that the basal metabolism drops to normal, but not below, within eighteen days after the resection of the adenomatous tissue, and there is no tendency to a recurrence of the hyperthyroidism.

Six patients have come under my observation who, following very extensive resection of the thyroid for combined adenomatous and colloid goiter, have a basal metabolism from 12 to 17 per cent below normal and a recurrence of multiple adenomas. These adenomas react to thyroxin as does colloid goiter. One of the patients has been under almost constant observation for two years. When the basal metabolism is brought to normal the adenomas, 5 cm. in diameter, almost disappear. She can estimate her basal metabolism within 5 per cent, if it is not elevated above normal, from the size of the adenomatous nodules.

While the hyperthyroidism may come on suddenly and its course may be marked by waves of high intensity, it is characteristic of the

disease to come on insidiously and for a long period, not infrequently for years, to run a course of low intensity, and to be brought to attention by the phenomena attributable to fatigue and by resulting degenerative changes, rather than by changes indicating a hyperthyroid state. Some patients may be hyperthyroid for many months either from hyperfunctioning adenomatous goiters or from the administration of thyroxin, and wholly unconscious of any departure from the normal status. Those of a nervous temperament, particularly the type prone to develop cardiac neuroses, are more apt to be disturbed.

The development of diffuse colloid goiter in man, other factors remaining constant, is determined by an equation taking into consideration the iodine available to the thyroid and the rate of exhaustion of thyroxin in the tissues. Infection of the organism, at least when attended with fever, probably increases the rate of exhaustion of thyroxin in the tissues. That infection of the thyroid can stimulate the gland to hyperfunction is indicated by a moderate degree of hyperthyroidism early in the history of patients having diffuse thyroiditis ultimately resulting in myxedema. That introduction of bacteria into the digestive tract is an important factor, if not the primary cause of endemic goiter, is fairly well established. As to how the organisms act in the host, there is no definite evidence. That the bacterial flora of the digestive tract may sufficiently interfere with the absorption of the small amount of iodine in the available diet is a possibility, particularly in areas in which this element is relatively small. The relation of the bacterial flora to the available iodine would well explain the geographic distribution of endemic goiter.

THE BASAL METABOLIC RATE IN HYPERTHYROIDISM*

WALTER M. BOOTHBY

By the term hyperthyroidism is meant the clinical syndrome resulting from the presence in the body of an excess of thyroxin, which Kendall has identified as the active principle of the thyroid gland, and which, according to Plummer,²⁴ "is a catalyst that accelerates the rate of formation of a quantum of potential energy in the cells of the organism." This syndrome is characterized by an increased basal metabolic rate, and by intoxication clinically evidenced by nervousness, tremor, tachycardia, loss in strength and weight, and in the later stages, myocardial disintegration.

FACTORS INFLUENCING BASAL METABOLIC RATE

Plummer²⁴ has proved the calorogenic action† of thyroxin by extensive basal metabolic rate studies, following its intravenous injection in myxedematous and normal persons, and also by partial removal of the thyroid gland from patients with hyperthyroidism. From the basal metabolic rate curves thus obtained it can be calculated that from 12 to 14 mg. active thyroxin must be present in the body to maintain the basal metabolic rate at the normal level, and that the rate of loss or destruction of the thyroxin is probably not far from 0.5 mg.

* Presented before the joint meeting of the Section on Practice of Medicine, the Section on Pharmacology and Therapeutics, and the Section on Pathology and Physiology at the Seventy-second Annual Session of the American Medical Association, Boston, June, 1921. Reprinted from the *Journal of the American Medical Association*, 1921, lxxvii, 252-255.

† Dr. Graham Lusk has requested that the term "specific dynamic action," previously used by Plummer and Boothby to indicate the calorific or heat producing power of thyroxin and epinephrin, be reserved to express the increase in heat production following the ingestion of a foodstuff, maintaining the sense of the term as originated by Rubner. The term "calorogenic action" has been suggested by Dr. Lusk, after consultation with Dr. Francis G. Benedict, to signify the specific stimulus to metabolism given by such substances as thyroxin and epinephrin.

daily. The average calorigenic action resulting from the intravenous injection of different amounts of thyroxin in sixty-nine cases of myxedema or hypothyroidism of varying degrees of intensity is summarized in Tables 1 and 2, and a characteristic curve is given in Figure 138, together with a curve illustrating the return to normal in the basal metabolic rate, following the removal of an adenoma from a patient having adenoma with hyperthyroidism. Therefore, pathologic variations in the basal metabolic rate are due, at least in dis-

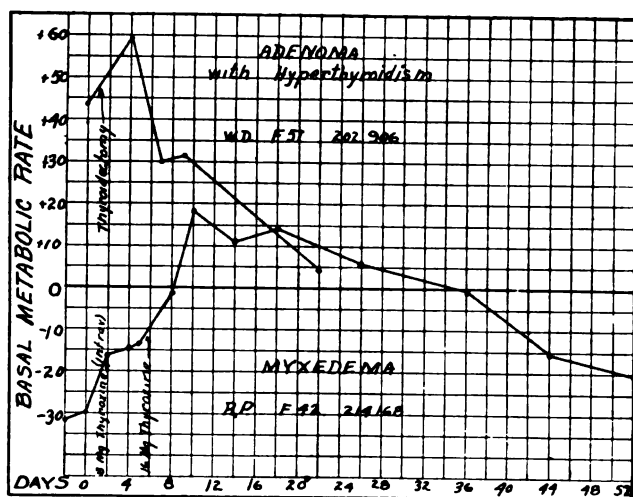


FIG. 138.—On the upper curve the basal metabolic rates of a patient with adenoma with hyperthyroidism are plotted showing the original preoperative rate and the immediate postoperative rise in the metabolic rate, followed by the drop to normal after partial thyroidectomy. The lower curve illustrates the effect on the metabolic rate of a myxedematous patient of two intravenous injections of 8 and 16 mg. of thyroxin, from which can be calculated the amount of thyroxin needed to bring such a patient to a normal metabolic rate; and therefore the presumable amount of thyroxin in the body, and also the rate at which the thyroxin is destroyed or eliminated.

orders of the thyroid gland, either to an increase or to a decrease in the normal quantity of thyroxin in the body, thus explaining the characteristic and fundamental alterations in the basal metabolic rate found in hyperthyroidism and in hypothyroidism.

However, other factors than the quantity of thyroxin in the tissues may exist which play a part in the maintenance of the normal basal metabolic rate and influence its abnormal fluctuations, especially of a temporary nature. Removal of the suprarenals has been shown by

TABLE 1
STATISTICAL STUDY OF 1,656 CASES OF GOITER*

	Adenoma.		Exophthalmic goiter.		
	Non-toxic.	Toxic.	Two ligations, rest, and thyroidectomy.	One ligation, thyroidectomy.	Thyroidectomy.
Number of cases studied.....	254	366	341	275	420
Average age, years.....	44	48	37	38	36
Average duration goiter, years.....	15.7	18.0	3.4	3.9	5.0
Average age at onset of goiter, years...	28	30	34	34	31
Average duration symptoms, years.....		1.8†	1.6	1.5	1.3
Average age at onset of symptoms, years.....		46	35	37	35
Cardiac decompensation:					
Positive, per cent.....	13	46	54	48	24
Probable, per cent.....	5	10	9	5	7
Exophthalmos, per cent.....	2‡	3‡	67	65	51
Thrills, per cent.....	4	5	63	58	39
Bruit, per cent.....	12	12	87	86	67
Weight, pathologic specimen, gm.....	187	152	59	55	51
Glycosuria, per cent.....	1	2	1.4	1	1
Blood pressure:					
Systolic (floor)§.....	141	158	150	146	141
Diastolic (floor).....	85	86	75	74	77
Pulse pressure (floor).....	56	72	75	72	64
Pulse rate (floor).....	91	107	125	121	113
Basal metabolic rate, per cent.....	2	30	65	53	33
Clinical diagnosis correct, per cent 	98	88	99	98	97

* Differential diagnosis of adenoma without hyperthyroidism (nontoxic adenoma), adenoma with hyperthyroidism (toxic adenoma), and exophthalmic goiter. The cases of exophthalmic goiter are divided into three groups depending on the surgical treatment: (1) two ligations, two to three months' rest at home and thyroidectomy, (2) one superior pole ligation followed by thyroidectomy, and (3) primary thyroidectomy.

† 1.8 represents the average duration since the onset of definite symptoms; however, it is possible to elicit a history of possible duration of 3.2 years, and in this respect it differs from exophthalmic goiter which has a much clearer cut onset.

‡ The exophthalmos was only slight in these cases; never more than degree 1 on a scale of 4, and corresponds to that so frequently seen in certain types of nephritis.

§ The blood pressures and pulse rates were those obtained at the time of the clinical examination with the patient sitting.

|| Accepting the report of the Section on Surgical Pathology made by fresh frozen section examination at the time of operation as correct, the previous clinical diagnosis was found to correspond as indicated. The close agreement between the pathologist's diagnosis of adenoma, on the one hand, and diffuse parenchymatous hypertrophy (exophthalmic goiter), on the other hand, and the respective clinical diagnoses is very striking; the pathologist, however, cannot distinguish adenomas that produce hyperthyroidism from those that do not.

TABLE 2

DURATION OF GOITER IN ADENOMA WITH AND WITHOUT HYPERTHYROIDISM AND IN EXOPHTHALMIC GOITER (1,656 CASES)

Duration, years.	Exophthalmic goiter, per cent.	Adenoma.	
		With hyperthyroidism, per cent.	Without hyperthyroidism, per cent.
From 0 to 0.9.....	42	17	10
From 1 to 1.9.....	15		
From 2 to 2.9.....	9		
From 3 to 3.9.....	6		
From 4 to 4.9.....	3	14	18
From 5 to 9.9.....	11		
From 10 to 14.9.....	4		
From 15 to 19.9.....	4		
20.....	5	43	37

Average duration of goiter in exophthalmic goiter..... 4.2 years
 Average duration of goiter in adenoma with hyperthyroidism..... 18.0 years
 Average duration of goiter in adenoma without hyperthyroidism..... 15.7 years

Aub² to cause a decrease in the basal metabolic rate, which may be brought back to normal by the slow intravenous injection of suprarenal extract, at the rate stated by Stewart and Rogoff to be the normal output in the body. Conversely, Boothby and Sandiford⁴ have shown that epinephrin possesses a calorogenic action in man when injected subcutaneously (0.5 c.c. of 1 : 1,000). However, the evidence is not yet conclusive that the suprarenal glands are concerned with the normal rate of resting cellular combustion, or that they are the primary cause of abnormal rates of any definite clinical syndrome, notwithstanding the fact that decreased rates have been reported in Addison's disease and following experimental suprarenalectomy.

The possible increased basal metabolic rate in active acromegaly, and the decreased rate in the syndrome known as hypopituitarism, suggest that alterations in the activity of the pituitary gland may change the metabolic level. There is, however, as yet little evidence that the secretion of any part of the pituitary gland is concerned with the normal rate of cellular combustion in the sense that it acts as a calorogenic agent. There are certain other diseases in which very occasionally an increased basal metabolic rate has been found; the cause of the increased heat production in these instances is not known.

At this meeting DuBois has shown that the increase in the basal metabolic rate accompanying febrile diseases follows van't Hoff's law

of the velocity of chemical reactions with temperature changes; it is about doubled for an increase of 10 degrees C.

A decrease in the basal metabolic rate is characteristic of myxedema and is due to the inability of the thyroid gland to supply a sufficient amount of thyroxin. A lowered basal metabolic rate has been consistently found in experiments in prolonged fasting, and in clinical conditions of inanition in which the food supply is decreased over a long period (stricture of the esophagus, cardiospasm, anorexia nervosa, and so forth); the mechanism producing this decreased rate is not known, yet it seems quite probable that it may be compensatory slowing down of the life processes in an endeavor on the part of the organism to prolong life on a minimum utilization of its stored food, and that the thyroid gland itself takes part in this decreased compensatory process, with a consequent reduction in the amount of thyroxin acting as a catalyst.

UNSTABLE FOUNDATION OF ENDOCRINOLOGY

While we recognize that there is a biologic interdependence not only of every organ but of every cell in the body, nevertheless we are able to measure quantitatively only the calorigenic power of the active principle of the thyroid gland; consequently we deprecate the tendency so much in evidence in current literature to parcel out to each ductless gland a certain definite yet entirely hypothetical power, and to build on such an unstable foundation the mammoth superstructure expressed in the term endocrinology.

ADENOMA WITH HYPERTHYROIDISM

Plummer²⁴ has shown that pure hyperthyroidism can be produced in a person by the administration of an excess of thyroxin, and that the syndrome thus produced cannot be distinguished from that caused by an overactive adenoma of the thyroid gland. In each case, either the discontinuance of the thyroxin or the operative removal of the adenoma ends the syndrome, and the patient rapidly returns to a normal condition, with a normal basal metabolic rate (Table 4). The characteristic symptoms of adenoma with hyperthyroidism are those that can be predicted from a knowledge of physiologic effects produced by a prolonged increase in the rate of cellular combustion; consequently, for many years Plummer²⁷ has spoken of the overfunctioning adenoma of

TABLE 3
AGE AND OCCURRENCE OF ADENOMA WITH AND WITHOUT HYPERTHYROIDISM AND EXOPHTHALMIC GOITER

Age.	Percentage of patients by decades having hyperthyroidism caused by (1) adenoma or (2) exophthalmic goiter.			Percentage of cases in each decade of (1) adenoma without hyperthyroidism, (2) adenoma with hyperthyroidism, (3) exophthalmic goiter.		
	Number of cases.	Adenoma, toxic.	Exophthalmic goiter.	Adenoma.		Exophthalmic goiter.
				Nontoxic.	Toxic.	
From 0 to 9.....	1	0	100	0	0	1
From 10 to 19.....	59	8	92	1.5	1	5
From 20 to 29.....	280	10	90	8	8	24
From 30 to 39.....	374	13	87	24	13	31
Below 40.....	714	...	...	33	22	61
From 40 to 49.....	358	30	70	33	29	24
From 50 to 59.....	253	46	54	27	32	13
From 60 to 69.....	75	77	23	6	16	2
From 70 to 79.....	2	100	0	0.5	1	0
Above 40.....	688	...	...	67	78	39
Number of cases.....	1,402	366	1,036	254	366	1,036
Average age.....		48	37	44	48	37

the thyroid as "adenoma with hyperthyroidism," and has recognized the disease as a clinical entity with a characteristic course and symptoms. In this condition the thyroid gland presents, on pathologic examination, discrete, single or multiple nodular adenomatous tumors in various stages of degeneration, surrounded by a definite capsule.

EXOPHTHALMIC GOITER

Until recently adenoma with hyperthyroidism has been confused with exophthalmic goiter, which is another pathologic condition of the thyroid gland, consisting of diffuse parenchymatous hypertrophy, symmetrically involving the entire gland. Clinically, exophthalmic goiter, like adenoma with hyperthyroidism, is characterized by an increased basal metabolic rate and, therefore, both diseases have in common the symptoms due to the increased rate. However, exophthalmic goiter has a different clinical course from adenoma with hyperthyroidism, and, in addition, certain peculiar and characteristic symptoms, one or more of which are present in varying degrees, such as exophthalmos, thrills and bruit, tendency to gastro-intestinal crises, and a peculiar type of

TABLE 4
EFFECT OF OPERATIVE TREATMENT ON 284 CASES OF EXOPHTHALMIC GOITER AND ADENOMA

	Exophthalmic goiter.										Adenoma.	
	Two ligations, rest at home, and thyroidectomy.					One ligation and thyroidectomy.					With hyperthyroidism.	
	Ten days.					Ten days.					Without hyperthyroidism.	
	Before treatment.	After second ligation.	After two months' rest.	After thyroidectomy.		Before treatment.	After first ligation.	After thyroidectomy.			Before treatment.	After thyroidectomy.
Basal metabolic rate, per cent.	+68	+51	+43	+20		+36	+39	+17		+8	+35	+6
Systolic blood pressure.	139	132	131	125		133	126	119		122	145	133
Diastolic blood pressure.	75	72	72	75		73	66	71		73	81	78
Pulse pressure.	64	60	59	50		60	60	48		49	64	55
Pulse rate.	122	114	108	93		116	106	92		86	102	79
Weight.	52.3	48.0	56.6	56.3		53.3	52.8	49.7		52.9		
Number cases in each group.	55					42					92	
						72					23	

nervousness. That we are dealing with two entirely distinct diseases in exophthalmic goiter and in adenoma with hyperthyroidism has been proved beyond reasonable doubt by Plummer,²⁷ by the difference in the mode of onset of the two diseases, the clinical course and duration of the symptoms, the physical findings, and, finally, the difference in the pathology of the thyroid gland. The differential points in the two diseases are strikingly shown in Tables 1, 2, and 3. To account for these differences, the most probable hypothesis is that in exophthalmic goiter not only are the thyroid cells producing an excess of thyroid hormone, but also the secretion so formed has some abnormal and peculiar chemical properties that produce the symptoms that differentiate it from pure hyperthyroidism. Kendall has suggested that probably there is, in exophthalmic goiter, a slight alteration in the structure of the thyroxin molecule.

The delay in the recognition of adenoma with hyperthyroidism as a disease distinct from exophthalmic goiter has been due in part to the fact that it was not at first recognized that small isolated areas of hypertrophic cells, such as may be found in some adenomatous thyroids, do not produce the clinical syndrome of exophthalmic goiter and, conversely, that diffuse parenchymatous hypertrophy may develop in a gland in which adenomatous tumors are incidentally present.

OPERATIVE PROCEDURE IN THE TWO DISEASES

Aside from the academic interest in differentiating adenoma with hyperthyroidism and exophthalmic goiter, the correct diagnosis is of great clinical importance because the times of onset, duration, course, and outcome are different; furthermore, the operative program is not the same in these two diseases. In adenoma with hyperthyroidism the operation is directed to the removal of the tumor, while in exophthalmic goiter the surgical procedures are planned to reduce, in the severer cases, the overactivity of the diffuse parenchymatous hypertrophied thyroid by successive steps: first, hot water injection, second, one or more ligations, and, finally, one or more partial thyroidectomies. In adenoma with hyperthyroidism preliminary ligation of the blood-vessels is seldom of benefit even in the severe cases, while in exophthalmic goiter the benefit from ligation is usually quite marked. Simple enucleation of the adenoma is almost invariably sufficient to cure the patient suffering from adenoma with hyperthyroidism; on the other hand, extensive resection of the greater part of both lobes and the

isthmus is necessary to reduce the activity of the hypertrophic parenchymatous thyroid of exophthalmic goiter within normal limits, and not infrequently a second and occasionally a third resection are necessary before the intensity of the intoxication is brought within the bounds of safety. The effect of operative treatment is illustrated in Table 4.

It is well known that the course of exophthalmic goiter proceeds in cycles of intensity with intervening periods of partial and occasionally total remission. Experience has shown that the dangers of any operative interference during the rising curve of intensity and at the peak, especially if associated with gastro-intestinal crises and loss of weight, are greater than during the stage of improvement. The curve of the basal metabolic rate in conjunction with the loss or gain in body weight of the patient are valuable mathematical expressions of the intensity and phase of the intoxication cycle. We have been unable to prove that the roentgen ray definitely influences the natural course of exophthalmic goiter.

DIAGNOSTIC VALUE OF BASAL METABOLIC RATE

Accepting the definition of hyperthyroidism as a clinical syndrome resulting from the presence in the body of an excess of thyroxin which increases the rate formation, and the conception that the basal metabolic rate serves as a fundamental classification of disease,⁷ it is obvious that a very sharp distinction can be drawn between mild cases of exophthalmic goiter and those conditions known as "effort syndrome," "disordered action of the heart," "cardiac neurosis," "nervous instability," "neurocirculatory asthenia" or "neurasthenia," which on superficial examination present some of the signs and symptoms of mild exophthalmic goiter, but in which the basal metabolic rate is normal, and which on close analysis can be shown not to be dependent on an excess in the body of the thyroid hormone. The basal metabolic rate is of particular diagnostic value in these cases when they are accompanied, apparently without causal relationship, by a colloid enlargement of the thyroid gland as so often occurs in the regions of endemic goiter.

VALUE OF VARIOUS TESTS

Confusion in the differential diagnosis of functional neurasthenia from mild exophthalmic goiter and adenoma with hyperthyroidism has

been increased during the last few years by the revival of the epinephrin hypersensitive test in a new guise by Goetsch.¹⁴ A series of studies by Peabody and his associates, and similar studies from our laboratory,⁶ have shown that there is no correlation between the intensity of the epinephrin reaction and the degree of hyperthyroidism as controlled by simultaneous studies of the basal metabolic rate; also, that the so-called positive epinephrin reaction is present in a large percentage

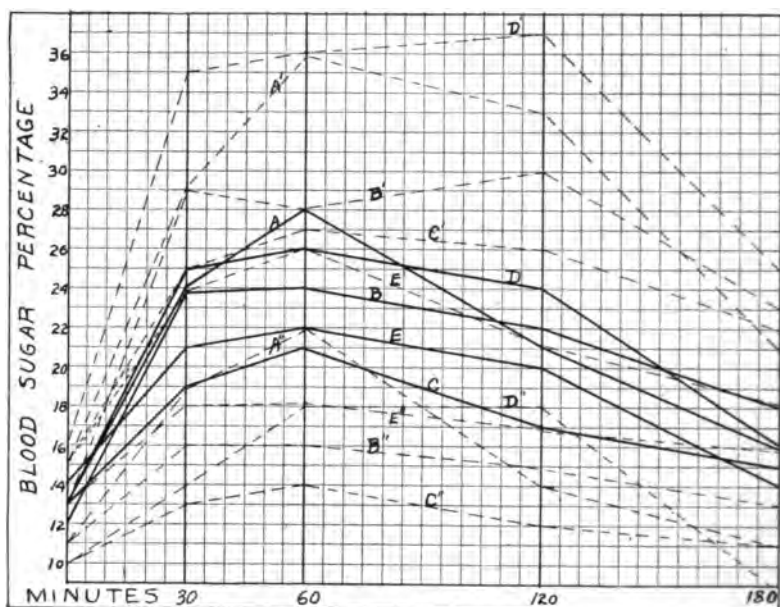


FIG. 139.—The heavy black lines represent the average blood sugar curves following the ingestion of 100 gm. of glucose in patients having various basal metabolic rates; the dotted lines represent the upper and lower limits of each group. A, A' and A'', average, upper and lower limits for seven cases with basal metabolic rates between +40 and +59 per cent; B, B' and B'', six cases between +11 and +39 per cent; C, C' and C'', ten cases between -40 and -11 per cent; D, D' and D'', sixteen cases above +60 per cent; E, E' and E'', four cases between -10 and +10 per cent.

of cases that are not hyperthyroid, and even occasionally in patients with myxedema. Studies on the action of epinephrin by Boothby and Sandiford⁵ show that there is not sufficient physiologic basis for the assumption that the reaction to the subcutaneous injection of an active principle of the suprarenal gland is indicative in clinical medicine of activity of the thyroid gland. The blood sugar curves as shown in Figure 139, following the ingestion of 100 gm. of glucose, have not been

sufficiently consistent in the different types of cases studied by us to be of diagnostic value, in spite of the fact that high and prolonged curves were more frequently found in patients with hyperthyroidism than in those with hypothyroidism.

CONCLUSIONS

The basal metabolic rate, which is a determination of the heat production in a person under standard conditions, serves as a measurement of the most fundamental process of life itself. Variations of the heat production and alterations in the body temperature are to be considered rightly a means of fundamental disease classification, and the basal metabolic rate serves as an accurate diagnostic aid in the recognition of the presence or absence of hyperthyroidism.

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CALORIGENIC ACTION OF THYROXIN*

HENRY S. PLUMMER AND WALTER M. BOOTHBY

The calorigenic action produced by the intravenous injection of different amounts of thyroxin in sixty-nine cases of myxedema or hypothyroidism of varying degrees of intensity is reported and characteristic curves shown.

TABLE I

AVERAGE INCREASE IN BASAL METABOLIC RATE FROM INTRAVENOUS INJECTION OF THYROXIN

Increase per mg.	2.8	Increase per mg. per sq. m.	4.7
Largest plus variation.	2.8 = 100 per cent	Largest plus variation..	2.9 = 60 per cent
Largest minus variation.....	1.8 = 64 per cent	Largest minus variation.....	2.9 = 60 per cent
Average variation....	0.7 = 25 per cent	Average variation....	1.1 = 23 per cent

TABLE 2

CALORIGENIC ACTION OF THYROXIN

Average basal metabolic rate.	Variation in calorigenic action depending on the original level of the basal metabolic rate.				Variation in calorigenic action depending on size of dose.			
	Average dose.	Increase per milli-gram.	Average dose per square meter.	Increase per milli-gram per square meter.	Average dose.	Increase per milli-gram.	Average dose per square meter.	Increase per milli-gram per square meter.
Above to -14.....	8.7	3.3	5.7	5.0	4.8	3.5	9.6	5.0
-15 to -19.....	9.1	2.3	5.1	3.9	6.9	2.8	5.2	5.0
-20 to -24.....	7.3	2.9	4.6	4.6	8.8	2.9	7.0	5.2
-25 to -29.....	10.9	2.8	6.2	5.0	11.2	3.3	9.3	4.8
-30 to -34.....	14.8	2.9	9.2	4.9	16.0	2.6	11.5	2.7
-35 and below....	15.5	3.0	8.6	5.1	24.0	1.6	13.2	3.0

As can be seen from Tables 1 and 2 and the dynamic curves (Fig. 140), the effect of 1 mg. of thyroxin given intravenously is an increase in the basal metabolic rate of 2.8 points; therefore a dose of 10 mg. can be predicted to increase the basal metabolism from -40 per cent to -12 per cent. The error of prediction is of slightly less magnitude

* Reprinted from the American Journal of Physiology, 1921, lv, 295-296.

if the dosage is based upon milligrams per square meter of body surface. The height of the metabolic reaction most frequently occurs on the eighth day.

Small intravenous doses of thyroxin repeated at short intervals have shown that less than 1 mg. daily is more than sufficient to replace any loss or destruction of thyroxin in the body, although the exact amount has not yet been definitely determined. However, by extrapolation of the descending part of the dynamic curve of thyroxin it can be esti-

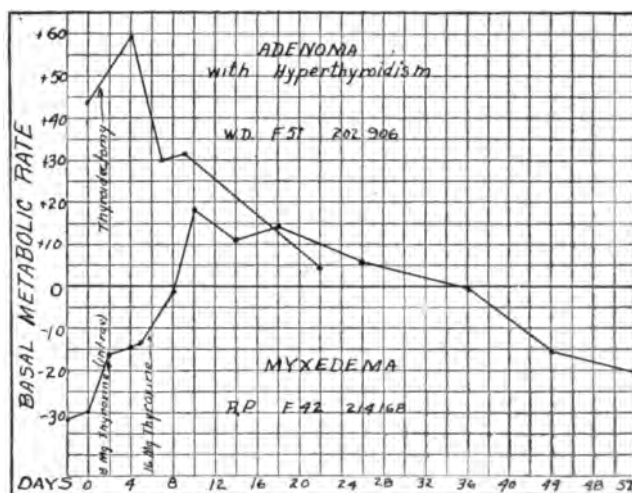


FIG. 140.—On the upper curve the basal metabolic rates of a patient with adenoma with hyperthyroidism are plotted showing the original preoperative rate and the immediate postoperative rise in the metabolic rate, followed by the drop to normal after partial thyroidectomy. The lower curve illustrates the effect on the metabolic rate of a myxedematous patient of two intravenous injections of 8 and 16 mg. of thyroxin, from which can be calculated the amount of thyroxin needed to bring such a patient to a normal metabolic rate; and therefore the presumable amount of thyroxin in the body, and also the rate at which the thyroxin is destroyed or eliminated.

mated that the rate of loss or destruction of the thyroxin usually ranges between 0.2 and 0.4 mg. daily in a myxedematous subject brought up to a normal basal metabolic rate; total metabolism rather than basal metabolism, however, probably governs the rate of thyroxin loss. From the thyroxin curves it can further be calculated that 12 to 14 mg. of active thyroxin must be present in the body to maintain the basal metabolic rate at the normal level. Pathologic variations in the basal metabolic rate are due, at least in most instances, either to an increase

or decrease of the necessary quantity, thus explaining the characteristic and fundamental alterations in the metabolic rate found in hyperthyroidism and in hypothyroidism.

If thyroxin is given by mouth the height of the metabolic reaction is usually not so great nor so constant as when given intravenously, probably due to its incomplete absorption from the gastro-intestinal tract. Therefore, the daily oral dosage necessary to maintain the metabolism at a normal level in a myxedematous person is distinctly larger than the calculated rate of elimination given above; the oral dosage is approximately 1.6 mg. daily.

The above data include the experiments reported by H. S. Plummer at various times since 1917, and the present averages agree essentially with those of his earlier series. Thyroxin undoubtedly has a calorogenic action increasing the metabolic rate in proportion to the quantity actively present in the body. Kendall has suggested the probability that its calorogenic action lies in aiding oxidation by rendering more readily available nascent oxygen atoms, which agrees with the theory of Plummer that "the active agent of the thyroid gland is a catalyst that accelerates the rate of formation of a quantum of potential energy in the cells of the organism."

SOME PHYSIOLOGIC AND CHEMICAL PROPERTIES OF THYROXIN*

EDWARD C. KENDALL

The observation made by Plummer, that there is a quantitative relationship between the amount of thyroxin administered and the increase in basal metabolic rate, has proved of very great importance in the study of the function of the thyroid. This test for thyroid activity has now been established in a large series of cases of high-grade myxedema, and the uniformity of the results over wide variations in the amounts of thyroxin administered establishes the value of this criterion for thyroid activity. It eliminates all the older criteria which have been based on the after-effects of the action of thyroxin and on clinical symptoms. It places the determination of thyroid activity on a quantitative basis, which cannot be said of any other ductless gland.

I wish to point out some of the characteristics of the influence of thyroxin on the metabolic rate. It has been shown that thyroxin has a latent period in practically all cases, and there is a slow building up of the reaction, which reaches the maximum on the ninth or tenth day after a single injection, and persists for from five to seven weeks.⁷ With regard to the latent period, it is evident that the presence of thyroxin within the tissues does not of itself determine the metabolic activity. Eventually the metabolic rate comes into equilibrium with the amount of thyroxin functioning, but time is an essential factor; a sudden increase in the amount of thyroxin does not immediately and spontaneously elevate the basal metabolic rate. This slowly developed and lasting effect of thyroxin is in striking contrast to the immediate and transient calorogenic action of epinephrin, which has recently been established by Boothby.

Another physiologic effect which I wish to emphasize is the action of thyroxin on the metamorphosis of the tadpole. This is most striking even in high dilution. A few hours suffice to bring about visible changes in the tadpole. The effect of other iodine compounds has been studied

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in relation to metamorphosis, and it has been found that iodine in some forms of combination, for example, as iodate, is entirely inert; other iodine compounds are only feebly active, for example, sodium iodide.^{3, 4} An inspection of the results obtained leads me to suggest that metamorphosis of the tadpole is accelerated by those iodine compounds only from which hypo-iodous acid can be formed directly or indirectly. These two types of physiologic response and the reactions on which they are apparently based will be discussed briefly.

It becomes almost axiomatic that the effect of thyroxine on the basal metabolic rate is essentially a catalytic reaction. The effect of thyroxine on metamorphosis, however, is not catalytic in nature, and it seems probable that a single stimulation or a stimulation lasting for a relatively short period is sufficient to initiate differentiation of the cells which then proceeds to completion. From a review of the experimental work on metamorphosis it seems established that the active agent directly responsible for the increased rate of metamorphosis is hypo-iodous acid. If the assumption is made that hypo-iodous acid is the active agent causing metamorphosis, the problem of explaining the two types of physiologic response would be simplified, provided it can be shown that the catalytic action of thyroxine also can be explained by a series of chemical results which involves the production of hypo-iodous acid.

Regardless of the structural formula of thyroxine, or even its empirical formula, it has certain chemical properties which are very suggestive in a consideration of the possible catalytic action of thyroxine. It has been observed from the very beginning of the isolation of thyroxine that it is exceedingly sensitive to reducing agents.⁵ If kept in the presence of metals, such as iron, zinc, and tin, the iodine is rapidly split off from the molecule. At a proper hydrogen ion concentration and temperature and in the presence of certain impurities, iodine is broken off from the thyroxine molecule. In a slightly alkaline solution of thyroxine iodine breaks out of the molecule, not as iodine or sodium iodide, but as sodium hypo-iodite. Finally, derivatives of thyroxine in which the hydrogen of the imino group is replaced by a larger group, such as the acetyl or ureid, are stable in acid and in alkaline solutions, but decompose spontaneously and with vigor at room temperature and with the hydrogen ion concentration of distilled water, liberating hypo-iodous acid. These reactions have been studied quantitatively and are very definitely established.⁶

The theory of oxidation in the animal organism has recently assumed more importance than ever before among physiologists and biochemists, and Weiland's theory of dehydrogenation is placed on a substantial foundation by the isolation of glutathione by Hopkins. Dakin, in the consideration of oxidation in the animal organism, refers to glutathione as acting in a catalytic manner. Its precise function is to lower the threshold at which dehydrogenation takes place.

Glutathione has been shown to react by taking up hydrogen, and later in the presence of molecular oxygen, giving up the hydrogen and being oxidized to its former state. It, therefore, becomes of interest to consider the thyroxin molecule in order to see if a series of chemical reactions could occur which would result in a similar reaction. In this connection it is apparent that the organic nucleus and the iodine are of equal importance for the catalytic functioning of thyroxin. The necessary and sufficient changes in the organic nucleus to promote such a catalytic action are: (1) a change in the valence of the nitrogen from 3 to 5, (2) the splitting out of hydriodic acid from the reduced benzene ring to form a double bond, (3) the closing of the pyrrole ring changing the nitrogen from a valence of 5 to 3, and (4) the addition to the double bond of the hydriodic acid which has in the interim been split off from the iodamine, giving off one atom of oxygen and restoring the structure to its original form. Whether the iodamine thus formed with the resulting production of hypo-iodous acid functions as a superoxidase or as an acceptor of hydrogen is not known and this knowledge is not essential to an understanding of the action. It seems probable, however, that the function of thyroxin is better explained as a substance lowering the threshold at which dehydrogenation is possible rather than assuming it to be a superoxidase. This catalytic production of hypo-iodous acid is sufficient to explain the effect of thyroxin on the basal metabolic rate.

In regard to the metamorphosis of the tadpole, it has been found that compounds, such as the acetyl and ureid, will produce metamorphosis almost as well as thyroxin, but these substances are without effect on the basal metabolic rate. This can be explained by the fact that in these substances hypo-iodous acid can be produced just as it can be formed from thyroxin, but the alteration in the organic nucleus prevents this reaction from being repeated and therefore no catalytic effect is evident.

If the production of hypo-iodous acid is the essential intermediate step in the action of thyroxin, both as a catalyst, increasing the basal

metabolic rate, and in initiating metamorphosis, then the significance and interpretations of all known chemical properties and physiologic effects of thyroxin and its derivatives are brought into harmony.

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THE SURGICAL MANAGEMENT OF TOXIC GOITERS*

JOHN DE J. PEMBERTON

The term "toxic goiter" includes exophthalmic goiter and hyperfunctioning adenomatous goiter. During the past decade the immediate and end-results of the surgical treatment of toxic goiters have improved greatly. The improvements can be attributed directly to advances in our knowledge and surgical management of the diseases, due chiefly to the work of C. H. Mayo, Crile, Plummer, Kendall, and others, and indirectly to the fact that the knowledge of the decreased surgical mortality and better end-results has led patients to seek surgical treatment before the disease has produced irremediable visceral changes.

The statistics on exophthalmic goiter quoted in this paper are based on 1,224 operations performed on 677 patients from July 1, 1920 to July 1, 1921. The statistics on hyperfunctioning adenomatous goiter are based on 281 operations on 281 patients during the same period. The diagnosis of exophthalmic goiter was made from the clinical history and findings and from the determination of the basal metabolic rate, and was corroborated in every instance in which gland tissue was removed by the pathologist's diagnosis of diffuse parenchymatous hypertrophy of the thyroid gland.

TWO FORMS OF EXOPHTHALMIC GOITER

Exophthalmic goiter may occur in two forms, the remittent and chronic. In the remittent form the onset is usually gradual, and the patient may not be aware of its presence until the occurrence of a mild exacerbation induced by shock, fright, sickness, overwork, and so forth. The symptoms gradually increase in severity, with or without the appearance of a goiter or exophthalmos, until a crisis occurs in which all the symptoms suddenly increase in severity and usually are accompanied by nausea, vomiting, diarrhea, and extreme debility. If the

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patient survives the crisis a period of partial remission of the symptoms follows which may persist for months, but usually is superseded again and again by waves of varying intensity. The remission may be complete and the patient symptomatically cured, the disease being quiescent, or the remission may be partial, in which case the patient becomes a semi-invalid. In the chronic form the disease slowly progresses from a gradual onset and runs an even, usually mild course uninterrupted by waves of exacerbation. The disease may begin as the remittent form and continue as the chronic. The longer the progress of the disease is allowed to remain unchecked, the more marked will be the visceral degenerations (heart, liver, kidney, and muscles).

THE SELECTION OF PATIENTS FOR OPERATION

Surgery is now the treatment of choice in the greater number of these cases. However, surgery is not indicated in all stages of the disease, and in the choice of the time to operate and the selection of the type of operation for the individual patient lies the real crux of the problem. Unfortunately there is no rule of thumb to govern the indications for operation that is applicable to all patients.

The high operative risk attendant on surgery of the thyroid in exophthalmic goiter is not due to the accidental causes incident to a major surgical procedure, such as hemorrhage, infection, and embolism, but to the acute intensity of hyperthyroidism induced by the operation and to the frequency of pulmonary complications due to the patient's lowered resistance. Naturally, then, our efforts should be directed toward preventing and controlling the postoperative reaction and toward building up the patient's resistance. While much may be accomplished by reducing the intensity of the reaction and by applying supportive measures, unhappily our means of actually checking its progress are very limited and usually the postoperative wave runs its natural course of about three or four days and is then checked by the patient's resistance. Our means of preventing the reaction lie in the technic of the surgical management and in the preliminary treatment of the graver forms of the disease.

During the past five years the routine estimation of the basal metabolic rate in all patients with toxic goiter has been of inestimable value to the clinician and surgeon in planning the management of these patients. The basal metabolic rate gives an "accurate mathematical index of the degree of functional activity of the thyroid gland." Aside

from its value as an aid in the differential diagnosis of goiters associated with neurosis, it is apparent that repeated estimations in a patient will indicate in mathematical terms the accurate progress or regression of the disease. Generally speaking, the basal metabolic rate is a relative index of the operability; that is, if the criterion of operability were based solely on the basal metabolic rate in a large group of cases a higher mortality might be expected in a group with rates above $+50$ per cent than in a similar group with rates below $+50$ per cent. The individual case cannot be judged by this alone. The basal metabolic rate represents the minimum heat production of the body and is essentially a measurement of the catabolic processes; it does not express the degree of anabolism. It is readily conceivable that the rates of anabolism and catabolism may be increased equally or unequally, so that either anabolism or catabolism may predominate. In the patient in whom anabolism predominates the increased heat production is maintained at the expense of the food intake and the body cells suffer only from their increased activity; in the catabolic type the increased heat production is maintained, to a large extent, by the stored body pabulum, the cells thus suffering in consequence. Clinically the pictures of the two states differ widely. The one patient is mentally alert, excitable, well nourished, flushed, warm skinned, of a normal or slightly decreased weight, with a good or ravenous appetite. The other is alert but apprehensive, pale or cachectic, showing marked loss in weight and strength, with a poor or normal appetite. These types vary in degree in different patients, and in the same patient one state may supersede the other. It is apparent that the operative risk is considerably greater in the patient with the catabolic type, the patient who has lost weight, even though the basal metabolic rate is less than in the other. Not infrequently patients return to the Clinic after double ligation and an extended period of rest at home greatly improved in every respect, with the surgical risk obviously diminished, but with a higher basal metabolic rate than on the previous visit. It is, therefore, evident that the basal metabolic rate as an index to the operability of a patient with exophthalmic goiter is valuable only when considered with the clinical history and findings.

The high operative risk clearly contraindicates operation for exophthalmic goiter in three phases of the disease; that is, during an impending crisis (evidenced by a steady rise in the basal metabolic rate and loss of weight), during a crisis, and immediately after a crisis. Added

risk is obviously encountered in patients with low-grade infections, such as tonsillitis, otitis media, pleurisy, and the like, in patients with marked lowered resistance, as evidenced by marked loss of weight and strength; in patients with dilated hearts, and in patients with visceral degeneration. About 1 per cent of all patients with exophthalmic goiter show some trace of glycosuria, but unless they have true diabetes the operative risk is not materially increased.

CLASSIFICATION OF PATIENTS ACCORDING TO TREATMENT

Surgically, all patients with exophthalmic goiter fall into one of three groups: (1) patients on whom a primary thyroidectomy can be performed with reasonable safety, (2) patient's concerning whom the wisdom of advising thyroidectomy is doubtful, and (3) patients in whom indications for extended observation or preliminary measures are clearly defined.

Group 1.—Primary thyroidectomy, unless contraindicated by some of the factors enumerated, is indicated in patients with mild or moderate hyperthyroidism whose basal metabolic rate is probably not more than +55 per cent, provided they are carrying the increased load well, as evidenced by their ability to perform their ordinary work requiring moderate exertion. It is important that the severity of the disease is not increasing. The degree of loss of strength and weight and the height of the basal metabolic rate taken separately are only relative criteria of the operability of patients with exophthalmic goiter, but taken together and in relation to the phase of the disease they become the basis on which an opinion is formed. Thus, in this group the greatest loss of strength was graded 4 on the basis of 1, 2, 3, 4, the greatest loss of weight was 55 pounds, and the highest basal metabolic rate was +90 per cent. The averages, however, for the group were: loss of strength 1.4, loss of weight 14 pounds, and basal metabolic rate +36 per cent.

Group 2.—In this group are patients whose basal metabolic rates are but slightly higher than those of the preceding group, but about whom doubt exists as to the advisability of recommending thyroidectomy, possibly because of recent loss of weight, marked or moderate weakness of the quadriceps, the presence of slight edema, or undue apprehension on the part of the patient. In this group ligation of the superior thyroid vessels is advised as a test. If no reaction follows, or if one of only mild severity, as evidenced by temporary increased tachy-

cardia, nervousness, and slight vomiting, the gland may be resected in from seven to ten days. However, if following ligation moderate or severe reaction develops, including marked restlessness, extreme tachycardia, vomiting, and possibly fever, a second ligation is indicated, and the patient is classified in Group 3. In Group 2 the greatest loss of strength was graded 4, the greatest loss of weight was 67 pounds, and the highest basal metabolic rate was +89 per cent. The averages, however, for the entire group were: loss of strength 1.65, loss of weight 19 pounds, and basal metabolic rate +51 per cent.

Group 3.—A certain number of patients with exophthalmic goiter who come to the surgeon are obviously in need of rest, close observation in a hospital, and possibly preliminary medical and surgical treatment before major surgery can be attempted. The principal indications may be enumerated: (1) patients, irrespective of their general appearance, who are carrying a high degree of hyperthyroidism, as evidenced by a high metabolic rate, of +70 per cent or higher; (2) patients in actual crises, or patients whose histories indicate progression of the disease; (3) patients who are extremely apprehensive; (4) patients who show marked weakness, indicated particularly by their inability to walk any distance or to climb steps; (5) patients with marked recent loss of weight; (6) patients with cardiac dilatation; (7) patients with evidence of chronic visceral changes; and (8) patients with chronic infection. By rest and close observation in these cases the phase of the disease may be determined or the patient may be tided over an actual crisis, an overworked myocardium restored, or an infection may be eliminated, and a certain number of these patients may then be classified in Groups 1 or 2. The greater number, however, owing to excessive hyperthyroidism, or to lowered resistance, as evidenced by marked loss of weight, strength, and endurance, must be restored to their balance by preliminary measures before resection of the thyroid gland can be attempted with safety. In some of the patients the effect of simple surgical procedures cannot be anticipated with any degree of accuracy. Accordingly it remains for the surgeon to feel his way, beginning with the simplest procedure, such as injection into the thyroid gland of quinin-urea or of boiling water, in order to test the patient's resistance to an acute exacerbation of hyperthyroidism. If reaction follows, the procedure is tried again after the complete subsidence of the reaction. If, however, no reaction follows, ligation of the superior thyroid vessels can usually be undertaken safely. In most instances

the exclusion of a possible dangerous reaction following ligation may be anticipated and the procedure undertaken with but slight risk.

It is a frequent observation that following any exacerbation of hyperthyroidism, whether due to the natural course of the disease or induced by operation, a diminution of the hyperthyroidism occurs in from five to ten days, as recorded by the basal metabolic rate, below the preexacerbation level. This is accounted for by the patient's increased tolerance or immunity, and with few exceptions the reaction to the second ligation is of diminished severity. However, if a very marked reaction follows the first ligation, especially if accompanied by great prostration and fever, the second ligation, unless postponed for several weeks until the patient has regained her strength, may prove fatal.

After the ligation of both superior thyroid vessels and a period of rest (three months) the patients with but few exceptions show a really remarkable improvement. There is great gain in strength, endurance, and weight (often equalling the amount lost after the onset of the disease). In this series the average weight gained was 20 pounds, and the average reduction in the basal metabolic rate was 27 per cent. In many instances the recovery is so nearly complete that the patient feels that further surgery is unnecessary, but operation for the resection of the thyroid gland should be insisted on, or a "recurrence" will most likely follow.

A small percentage of patients who return after ligations will not be sufficiently improved to warrant undertaking a thyroidectomy with reasonable risk. The failure to gain may be accounted for in most instances by (1) continued overexertion or mental stress, (2) an intercurrent infection, (3) visceral degenerative changes, or (4) the failure actually to have ligated the superior thyroid artery. The difficulties encountered in correctly handling this small group of patients present a most perplexing problem to the surgeon. After further rest some patients show improvement spontaneously; others improve after "religations" of the superior or inferior thyroid arteries. Roentgen-ray treatment has been tried with indifferent success. Many of these patients are semi-invalids and show decided visceral degenerative changes, the effect of the long-continued hyperthyroidism. The limits of remedial measures beyond partial ablation of the thyroid gland are obviously restricted, and in consequence the patients cannot be made good risks; they constitute, therefore, the largest proportion of the

mortality group, and if the surgeon is working with an eye on the mortality record he is justified in refusing to operate. On the other hand, the operation, in many instances, is justifiable and indicated, for after the progress of the disease has been checked by a partial thyroidectomy many of these patients live happy and useful lives for many years. In this group (Group 3) the greatest loss of strength was graded 4, the greatest loss of weight was 77 pounds, and the highest basal metabolic rate was +129 per cent. The averages for the group were: loss of strength 2.22, loss of weight 22 pounds; and basal metabolic rate +63 per cent.

OPERATIVE PROCEDURES

As I have indicated, much may be accomplished by the preoperative preparation of patients who are poor risks. Often rest in bed for a week or ten days will bring about decided improvement and materially change the operative risk. It must be emphasized, however, that if rest in bed is prolonged over several weeks the patient's strength is lessened, and one may often be deceived with regard to the operability by the appearance of the patient in bed. It is most desirable, therefore, to have the patient up and around for a week or more before the final decision is made. Digitalis is indicated in patients with decompensated and fibrillating hearts.

Two important considerations often overlooked in the medical management of patients with exophthalmic goiter are the necessity for the increase in the fluid and food intake. Increased consumption of fluids aids materially in the elimination of the by-products of metabolism and of heat through evaporation. Boothby and Sandiford have shown by recent experiments that a patient with moderate hyperthyroidism at rest in bed requires higher caloric intake than a person doing moderate muscular work, so that the necessity of maintaining an easily assimilable diet becomes apparent.

Anesthesia.—Local anesthesia, or local combined with as little general anesthesia (gas oxygen or ether) as is possible to satisfy the patient, is safest for patients with exophthalmic goiter. Although these patients are nervous by reason of their disease, their confidence is easily acquired, and with but few exceptions they are eager for operation. It is decidedly advantageous to have the opportunity of observing patients who are poor or doubtful risks, awake on the operating table, and if occasionally a patient loses entire self-control or becomes extremely

apprehensive, a procedure milder than the one originally planned is indicated. Long general anesthesia of any kind tends, temporarily at least, to lessen the patient's resistance, and its effect, therefore, is only another obstacle to be overcome by an already overburdened organism.

OPERATIVE TECHNIC

Ligation.—The operative technic of ligation of the superior thyroid vessels and resection of the thyroid gland is well standardized. I shall

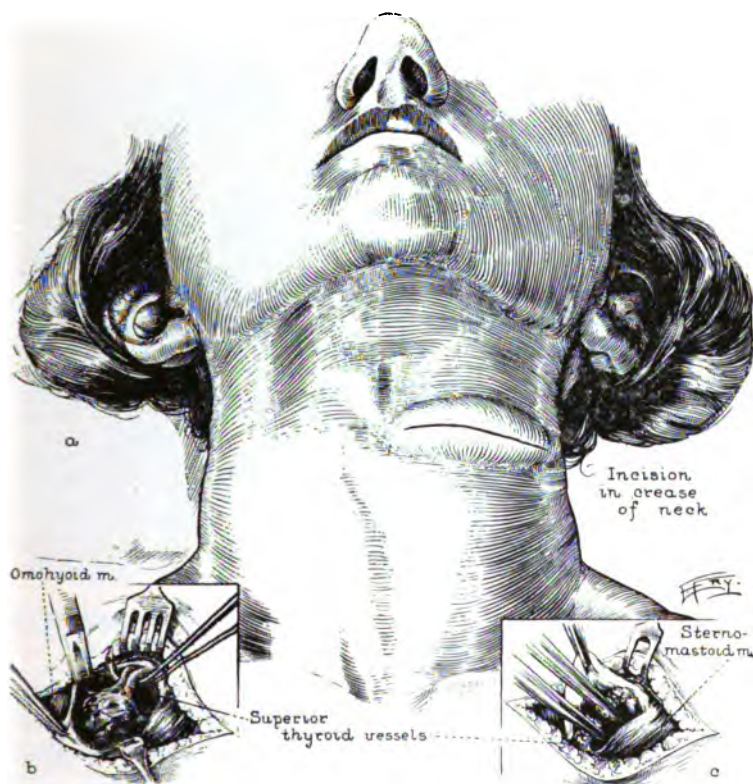


FIG. 141.—a. The incision is outlined by the needle in the crease of the neck before the superficial structures are injected. b. Fascia between the omohyoid and sternohyoid muscles divided and the ligature carrier passed beneath the superior thyroid vessels. c. The superior thyroid artery and vein divided and ligated.

emphasize only a few points of special importance (Fig. 141). A transverse incision, about 4 cm. long, in the line of the natural crease in the neck at the level of the thyroid cartilage gives ample exposure and

from its value as an aid in the differential diagnosis of goiters associated with neurosis, it is apparent that repeated estimations in a patient will indicate in mathematical terms the accurate progress or regression of the disease. Generally speaking, the basal metabolic rate is a relative index of the operability; that is, if the criterion of operability were based solely on the basal metabolic rate in a large group of cases a higher mortality might be expected in a group with rates above +50 per cent than in a similar group with rates below +50 per cent. The individual case cannot be judged by this alone. The basal metabolic rate represents the minimum heat production of the body and is essentially a measurement of the catabolic processes; it does not express the degree of anabolism. It is readily conceivable that the rates of anabolism and catabolism may be increased equally or unequally, so that either anabolism or catabolism may predominate. In the patient in whom anabolism predominates the increased heat production is maintained at the expense of the food intake and the body cells suffer only from their increased activity; in the catabolic type the increased heat production is maintained, to a large extent, by the stored body pabulum, the cells thus suffering in consequence. Clinically the pictures of the two states differ widely. The one patient is mentally alert, excitable, well nourished, flushed, warm skinned, of a normal or slightly decreased weight, with a good or ravenous appetite. The other is alert but apprehensive, pale or cachectic, showing marked loss in weight and strength, with a poor or normal appetite. These types vary in degree in different patients, and in the same patient one state may supersede the other. It is apparent that the operative risk is considerably greater in the patient with the catabolic type, the patient who has lost weight, even though the basal metabolic rate is less than in the other. Not infrequently patients return to the Clinic after double ligation and an extended period of rest at home greatly improved in every respect, with the surgical risk obviously diminished, but with a higher basal metabolic rate than on the previous visit. It is, therefore, evident that the basal metabolic rate as an index to the operability of a patient with exophthalmic goiter is valuable only when considered with the clinical history and findings.

The high operative risk clearly contraindicates operation for exophthalmic goiter in three phases of the disease; that is, during an impending crisis (evidenced by a steady rise in the basal metabolic rate and loss of weight), during a crisis, and immediately after a crisis. Added

risk is obviously encountered in patients with low-grade infections, such as tonsillitis, otitis media, pleurisy, and the like, in patients with marked lowered resistance, as evidenced by marked loss of weight and strength; in patients with dilated hearts, and in patients with visceral degeneration. About 1 per cent of all patients with exophthalmic goiter show some trace of glycosuria, but unless they have true diabetes the operative risk is not materially increased.

CLASSIFICATION OF PATIENTS ACCORDING TO TREATMENT

Surgically, all patients with exophthalmic goiter fall into one of three groups: (1) patients on whom a primary thyroidectomy can be performed with reasonable safety, (2) patient's concerning whom the wisdom of advising thyroidectomy is doubtful, and (3) patients in whom indications for extended observation or preliminary measures are clearly defined.

Group 1.—Primary thyroidectomy, unless contraindicated by some of the factors enumerated, is indicated in patients with mild or moderate hyperthyroidism whose basal metabolic rate is probably not more than +55 per cent, provided they are carrying the increased load well, as evidenced by their ability to perform their ordinary work requiring moderate exertion. It is important that the severity of the disease is not increasing. The degree of loss of strength and weight and the height of the basal metabolic rate taken separately are only relative criteria of the operability of patients with exophthalmic goiter, but taken together and in relation to the phase of the disease they become the basis on which an opinion is formed. Thus, in this group the greatest loss of strength was graded 4 on the basis of 1, 2, 3, 4, the greatest loss of weight was 55 pounds, and the highest basal metabolic rate was +90 per cent. The averages, however, for the group were: loss of strength 1.4, loss of weight 14 pounds, and basal metabolic rate +36 per cent.

Group 2.—In this group are patients whose basal metabolic rates are but slightly higher than those of the preceding group, but about whom doubt exists as to the advisability of recommending thyroidectomy, possibly because of recent loss of weight, marked or moderate weakness of the quadriceps, the presence of slight edema, or undue apprehension on the part of the patient. In this group ligation of the superior thyroid vessels is advised as a test. If no reaction follows, or if one of only mild severity, as evidenced by temporary increased tachy-

third of a normal lobe will prevent the occurrence of hypothyroidism. The advantage of leaving the posterior portion of the gland on either side is that it will serve as a buffer between the field of operation and the parathyroid bodies and the recurrent laryngeal nerve which lie behind.

After the resection of one lobe it is essential that the forceps be tied off before the other lobe is resected; otherwise the forceps may be pulled off accidentally, followed by bleeding, with staining of the opera-

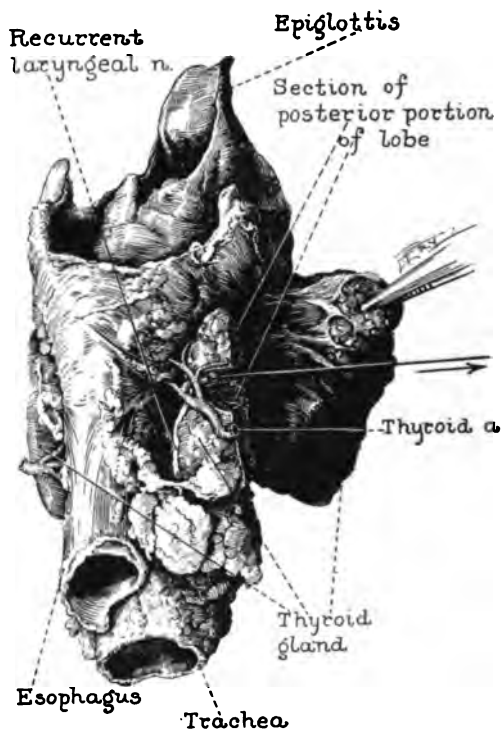


FIG. 144.—The thyroid gland sectioned and the posterior portion divided to expose the close relation of the recurrent laryngeal nerve and the branches of the inferior thyroid artery. Traction on the vessel branch pulls the nerve forward.

tive field and retraction of the vessel. In checking such bleeding injury to the important structures may occur, especially if there is a retraction of the main internal branch of the inferior thyroid artery which runs up between the trachea and the inner margin of the lobe of the thyroid (Fig. 144). The cut end of this vessel will lie very close to the recurrent laryngeal nerve. If on account of the extreme friability and vascularity of the goiter the resection of one lobe has consumed consider-

able time it is often wise to conclude the operation, and, if indicated, to resect the remaining lobe at a later date. However, in this series a double resection was performed in all except six of the cases.

Crile's plan of packing the wound with gauze in patients who are obviously poor risks has proved to be a valuable addition to the operative technic. The method used in the Mayo Clinic consists in packing the wound with two long strips, 2.5 cm., of sterile gauze. The wound is closed in the usual manner, permitting the ends of the gauze to protrude through the middle of the skin incision. A rubber tube is also inserted to drain off the serum not absorbed by the gauze. Better drainage is promoted and certainly wound absorption is considerably lessened. The drains may be removed in from twenty-four to forty-eight hours.

POSTOPERATIVE MANAGEMENT

In the postoperative management of patients with exophthalmic goiter the paramount necessity of administering fluids and more fluids should always be borne in mind. Immediately after the operation saline or glucose (5 per cent solution) should be given by rectum, or, if the patient is suspected to be a poor risk or is vomiting persistently, fluid should be given subcutaneously. The patient's ability to take fluid by mouth is an encouraging sign, and the prevention of gastro-intestinal upsets should always be considered in prescribing any accessory treatment. As I pointed out, food is important, but caution must be observed in pushing it too early because of the danger of upsetting the gastro-intestinal tract. The elimination of body heat by ice-bags and packs, as advocated by Crile, is valuable. Morphine should be used only to control restlessness; its too liberal use may be followed by nausea and vomiting. Digitalis is indicated in patients with fibrillating hearts, but it should not be continued at the expense of the gastro-intestinal tract. Inhalations of steam often prove very soothing in relieving excessive tracheal mucus.

In our experience "recurrences" and a lack of that improvement normal to the majority of patients are due to one of four factors: (1) too early resumption of muscular exertion (overwork) and mental stress, (2) infection (recurrent), (3) failure to remove a sufficient amount of thyroid gland, and (4) irreparable visceral changes. The first factor is preventable; the patient should always be advised not to resume strenuous work for a year or longer. Although the cause of the disease

is not known, the frequent presence of foci, and the fact that its onset often follows infections, such as influenza and tonsillitis, prove that infection must be an important factor. The elimination of all foci should be a routine precaution. In this series the onset of the disease followed influenza in 151 cases (22 per cent). A history of tonsillitis and septic tonsils was noted in 367 patients (55 per cent). Included in this series are fifty-six patients (8 per cent) with recurrent symptoms of exophthalmic goiter, of whom thirty-nine were females and seventeen males.

HYPERFUNCTIONING ADENOMATOUS GOITER

The history of a patient with hyperfunctioning adenomatous goiter differs widely from that of a patient with exophthalmic goiter. In the former the symptoms of hyperthyroidism do not occur on the average until about fourteen years after the appearance of the goiter, and their onset usually is insidious. Often the patient is unaware of the presence of the goiter and seeks medical advice only because of the visceral degenerative changes caused by the long-continued hyperthyroidism. There may be a relatively sudden onset, however, usually induced by an intercurrent infection or by the administration of iodine. The disease as a rule is mild, but progressive, and is seldom, if ever, interrupted by a spontaneous remission of symptoms. As pointed out by Plummer, the clinical picture may resemble either the syndrome of cardiovascular disease or that of true exophthalmic goiter.

Surgical management.—Except in the occasional patient who shows evidence of marked loss of weight and strength associated with a high degree of hyperthyroidism very little can be gained by preliminary surgical measures, such as ligations. In all of these patients, however, the preoperative medical measures and the strict operative requirements outlined for the patients with exophthalmic goiter are of equal importance.

MORTALITY

From July 1, 1920 to July 1, 1921, 1,954 patients with goiter were operated on in the Clinic. One hundred one had ligations only. Eighteen hundred fifty-three patients had partial thyroidectomies, in 465 of whom the thyroidectomy was preceded by one or more ligations. Thirty-five patients died, a mortality of 1.78 per cent. Eight of the 996 patients with simple goiter unassociated with hyperthyroidism died,

a mortality of 0.8 per cent. Four of the 281 patients with hyperfunctioning adenomatous goiter died, a mortality of 1.4 per cent. Twenty-three of 677 patients with exophthalmic goiter on whom 1,224 operations were performed (ligations and thyroidectomies) died, a mortality of 1.87 per cent by operations and 3.39 per cent by patients. Fourteen of the patients (2.39 per cent) were of the 585 who had thyroidectomy, and nine (1.4 per cent) were of the 639 who had ligations. Five (22 per

TABLE 1

TWELVE HUNDRED TWENTY-FOUR OPERATIONS ON 677 PATIENTS WITH EXOPHTHALMIC GOITER

	Operations.	Patients.	Males.	Females.	Average.							Per cent.			Previous thyroidectomy.
					Age, years.	Duration of goiter, months.	Duration of hyperthyroidism, months.	Loss of strength, graded 1, 2, 3, 4.	Loss of weight, pounds.	Pulse rate.	Basal metabolic rate, per cent.	Vomiting.	Diarrhea.	Edema.	
Group 1..... Primary thyroidectomy.*	212	212	42	170	36.5	43	33	1.40	14	111	+36	21	29	30	47
Group 2..... One ligation followed by thyroidectomy.	224	183	32	101	36.5	27	15	1.65	19	117	+51	22	25	31	8
Group 3..... Two ligations, rest, and thyroidectomy.	577	240	84	248	35.6	33	17	2.22	22	124	+63	26	31	46	1
Ligations†.....	171	92													
Averages.....	1224	677	168	519 (1:3+)	36.2	35	22	1.75	18	117	+50	23	28	36	56 8%

* The term "primary thyroidectomy" in this paper denotes the resection of the thyroid gland without preliminary surgical preparation. It will be noted that forty-seven patients with recurrent exophthalmic goiter are included in this group.

† Ninety-two patients have not yet returned for thyroidectomy.

TABLE 2

TWO HUNDRED EIGHTY-ONE OPERATIONS ON 281 PATIENTS WITH HYPERFUNCTIONING ADENOMATOUS GOITER

Operations.	Patients.	Males.	Females.	Average.				Per cent.		
				Age, years.	Duration of goiter, years.	Duration of hyperthyroidism, months.	Basal metabolic rate, per cent.	Edema.	Cardiac dilatation.	Auricular fibrillation.
281	281	39	242	46.7	15.5	2.2	+34.1	37	26	7

TABLE 3
HYPERFUNCTIONING ADENOMATOUS GOITER—DATA RELATING TO FOUR DEATHS

Case.	Sex, Age.	Duration of goiter, years.	Duration of hyperthyroid- ism, years.	Loss of weight, pounds.	Loss of strength graded 1, 2, 3, 4.	Pulse.	Basal metabolic rate, per cent.	Edema.	Fibrillation.	Myocardial degen- eration, clinical diagnosis.	Death after opera- tion.	Clinical cause of death.	Findings at necropsy.
A335687	F. 56	12	0.25	?	2	128	+50	+	+	+	36 hrs.	Hyperthyroidism. Myo- cardial degeneration.	Chronic nephritis; hem- orrhage in endocardium of the left ventricle.
A361539	F. 60	20	1	6	1	108	+20	+	-	-	56 hrs.	Pneumonia.	Bilateral lobar pneu- monia.
A361356	F. 61	30	10	38	3	104	+37	+	+	+	38 hrs.	Myocardial degenera- tion.	Myocardial degeneration; bronchopneumonia.
A323964	F. 69	2	2	?	3	118	+49	+	+	+	7 days.	Pneumonia.	Bronchopneumonia; nephritis; arterioscle- rosis (marked).
Averages Age...	 61.2	16	3.3	22	2.25	116	+39	100%	75%	75%			

cent) of the patients who died had recurrent goiter; they represent 8.9 per cent of the fifty-six patients in whom the disease recurred. The deaths were due to three main causes: (1) accidental causes, three patients; (2) intense hyperthyroidism, seven patients; and (3) moderate hyperthyroidism plus pulmonary complications due to the patient's lowered resistance incident to the long-continued progress of the disease or to some intercurrent cause, such as hemorrhage or infection, twelve patients. In one patient the operation failed to check the progress of the disease. The deaths due to severe hyperthyroidism are preventable to a large extent; either an error is made in selecting the patient for operation or in selecting the operation for the patient. If patients who are recognized as poor surgical risks are accepted for operation a higher mortality rate must be looked on as unavoidable (Tables 1, 2, and 3).

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A CONSIDERATION OF THE TREATMENT OF LESIONS OF THE THYROID GLAND*

E. STARR JUDD

For many years the thyroid gland was believed to function as an external protection to the larynx and trachea. Some observers believed that it emptied by a duct into the larynx, or into the pharynx or esophagus, and so had some influence on digestion. It was also believed to have something to do with the control of the circulation to the brain by direct influence on the carotid arteries. Most of these hypotheses were undoubtedly fanciful. We have only recently come to regard this ductless gland of great importance in metabolism. Our knowledge of the function of the thyroid has been obtained largely from a study of the results of total removal of the gland and a study of persons whose thyroids had never functioned.

The absence of the thyroid produces a syndrome termed myxedema or hypothyroidism. Children with total absence of thyroid function are known as cretins; in development they never reach the stage of puberty. After complete thyroidectomy the rate of metabolism is very greatly reduced; the growth of the osseous system is arrested, especially in the long bones, the skin becomes myxedematous, and the intellect is disturbed. If the thyroid is removed from young animals the skeletal development is retarded. This is especially noticeable in the nervous system and the genital system. The skin becomes infiltrated with mucinoid substances and is dry and rough. The hair and nails are brittle. If the thyroid is removed from an adult animal the results are the same except that the skeleton is already fully developed and does not change.

Very little has been accomplished to change the condition of cretinism in the human being. Some of the difficulties that result from the absence of the thyroid gland can be overcome by the administration of thyroid extract, or of thyroxin, the active principle of the gland. It

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seems to me that the greatest difficulty arises from the fact that cretinism is not recognized until the condition is of long standing. A great deal might be accomplished if it were possible to recognize the condition early and institute treatment at once. Most cretins are found in institutions for the feeble-minded and are several years old before any treatment is started. The change that occurs after the prolonged use of thyroid gland products is very striking, but this improvement continues only to a certain point. Many of the patients improve under the treatment and are able to walk and get about, and some of them grow several inches in height and seem brighter. At this stage there is a disappointment; apparently no matter how long the treatment is continued or what dosage is used, no further change can be made. In a few cases we have transplanted normal thyroid tissues, and in some, the thyroid tissue from a hyperplastic thyroid of a patient with exophthalmic goiter, but apparently with similar results.

Many cretins have adenomas and cysts in the thyroid. Sometimes the cysts become quite large and in several instances we have enucleated them with as little disturbance to the glandular tissue as possible, but the procedure has not offered much encouragement. Much more is accomplished with the myxedematous patient who at some time has had a normally functioning thyroid gland than with the cretin. All the changes which have taken place in the skin, hair, and nails, as well as the facial expression and mental condition, return to normal in a very short time after thyroid products are administered.

Myxedema is undoubtedly much more common than we realize, and unless we are constantly mindful of its evidences it is not difficult to overlook the real condition. Quite often it is present when there is no discernible lesion in the thyroid and no history of former trouble. It is sometimes seen in patients in whom there has been a long-standing adenomatous or colloid goiter, and not infrequently in those in whom apparently there has been hyperthyroidism at some previous time. I have seen several cases which followed what apparently in the beginning was thyroiditis.

Postoperative myxedema is extremely rare. For many years we believed we had never seen myxedema following thyroidectomy, but since we are now better able to recognize the condition we believe that some deficiency in the thyroid function occasionally follows operation on the gland. This, of course, can be best determined by an estimate of the basal metabolic rate after the operation. We found that it

was not unusual for the basal metabolic rate to drop after partial thyroidectomy, but that the drop apparently had no influence on the convalescence, and that frequently there was no clinical evidence of insufficiency in thyroid function. Apparently in operating for goiter, if the small piece of thyroid tissue is preserved with a good blood and nerve supply, insufficient thyroid function will not result. It seems to me this is the better way to determine the amount of thyroid gland that must be saved in subtotal thyroidectomies, rather than to designate a quarter or a sixth or a tenth of the gland, or of one lobe. Experimentally, a dog develops just as quickly and completely with all of the thyroid gland removed except one small viable piece as with the entire gland. Following the employment of roentgen-ray exposures in the treatment of lesions of the thyroid some cases of myxedema and some of tetany are being reported.

The tetany following operations on the thyroid is an interesting study. The syndrome is the same which may occur under other circumstances. Last year we observed two cases of gastric tetany following gastro-enterostomy for ulcers of the stomach. Apparently the conditions were synonymous, and in the one instance the patient's response to the treatment was the same as that following treatment for tetany with goiter. Tetany is much more common than myxedema following operations on the thyroid, although it does not occur in more than 0.25 to 0.5 per cent of all cases. It is more liable to follow secondary operations when partial thyroidectomies have been performed, possibly some years before, and the second operations are performed for recurrence of thyroid enlargement. In my experience the symptoms almost always begin by a sensation of stiffness in the fingers about the third day after the operation. It is difficult for the patient to raise fingers to the mouth or to hold anything. These symptoms may pass off in a few hours or a day, possibly after one or two doses of morphin, or the condition may gradually progress until the contractions involve not only the fingers but the muscles of the hands and arms, and sometimes they become general. Cases in which this condition has resulted fatally have been reported, although in our series of approximately twenty cases there have been no deaths. One patient who had a suppurative pericarditis as well as tetany did not recover, but we were able to control the contractions. In one of my patients I was obliged to ligate both inferior thyroid arteries at the same operation; this patient developed tetany. All of the circulation to the

parathyroids come from the inferior thyroid artery, so that when both of the inferior vessels are ligated at the same time the parathyroids are deprived of their circulation. The tetany in this case persisted for seven weeks; it then subsided and there was no return of the symptoms. Collateral circulation was undoubtedly established and the parathyroids resumed their function. I believe that all patients should have intravenous injections of calcium lactate, 10 c.c. of 5 per cent solution in 100 c.c. salt solution at the time of onset. The calcium lactate administered by mouth, through the bowel, or subcutaneously controls these spasms, although several doses at intervals may be required before the contractions stop. By the intravenous administration all symptoms usually subside within half an hour. Often one intravenous treatment is all that is necessary, although if there is any tendency to recurrence the dose should be repeated. Undoubtedly these cases of postoperative tetany are caused by a disturbance of the blood supply or nerve supply to the parathyroids at the time of the operation or by trauma to the parathyroid gland itself; therefore symptoms persist until the gland recovers from the trauma or until collateral circulation is established.

In all cases the patient may be assured that after thyroidectomy normal mentality and all normal functions will be maintained. In performing the thyroidectomy we always endeavor to preserve any apparently normal thyroid tissue.

For purposes of treatment and other considerations enlargements of the thyroid can best be considered in five groups. In the first group are adolescent goiters, in the second group, mechanical goiters, in the third group, toxic goiters, in the fourth group, inflammations, and in the fifth group, malignant goiters.

Group 1.—The adolescent or physiologic goiter in former years offered many difficulties in diagnosis. The enlargement in the thyroid is general throughout the gland and may attain considerable size. There may be a few small associated adenomas, but usually the enlargement is due to an increase in the colloid in the gland. The patient at this time in life is liable to be nervous and to have tremor, so that it is most important to make sure whether the condition is hyperthyroidism or whether the signs are all due to the adolescence. In many cases the distinction can be made by clinical evidence alone, because in adolescent goiter there is no loss of weight or strength, and the tremor differs from that with hyperthyroidism. It is most important to dis-

tinguish the two types because the girl in adolescence should not be operated on, even if we believe the symptoms to be due to a slight overactivity of the thyroid. If there is true hyperthyroidism surgery is the method of treatment preferred. In case of doubt conservative measures should be employed first. If the metabolic rate changes greatly and particularly if there is a marked loss of body weight, the condition may quite definitely be termed true hyperthyroidism. In some instances the adolescent goiter continues to enlarge, the colloid deposits increase, adenomas form in the gland, and the condition may become a mechanical goiter.

Group 2.—The mechanical goiter produces symptoms only by pressure and interference with the surrounding structures. Usually it is large and troublesome because of its size, although a small adenoma may produce more difficulty than a large one, or two small tumors may be placed so as to cause great interference. Usually pressure on the trachea causes difficulty in breathing; this is the first symptom, particularly if the patient has a cold. Pressure may be made on the pharynx or esophagus and produce trouble in swallowing, or it may be made on the larynx or recurrent nerves, causing a disturbance in the voice. The larynx and trachea may be markedly displaced by irregular enlargements in the thyroid. The circulation is often interfered with, the superficial vessels over the lower neck and chest are markedly dilated, compensating for the deep pressure.

Group 3.—There are two distinct types of toxic goiters, both of which may cause mechanical interference; they are chiefly disturbing because of the so-called toxemia which they produce. This toxemia is a result of overactivity of certain elements of the thyroid or the result of the absorption of some new product from the thyroid into the circulation. In some of the toxic cases in which there is a definite obstruction to the air passages the toxic features may be produced by a sub-oxidation, but, on the other hand, many of the most toxic cases show no mechanical interference.

Exophthalmic goiter is usually toxic from the beginning. The gland is generally enlarged and hyperplastic, and accompanied by exophthalmos. The second type of toxic goiter is usually a so-called innocent or possibly adenomatous goiter that has been in existence for an average of from nineteen to twenty years when the signs of hyperthyroidism develop. Exophthalmos is not common with adenoma with hyperthyroidism and the other features are different from those in

exophthalmic goiter, but there is much evidence of toxemia and a severe general disturbance. The actual disturbance of function and the degeneration of tissue are more marked than in cases of exophthalmic goiter. Any form of iodine administered to these patients exaggerates all symptoms; this treatment frequently seems to help the patient with exophthalmic goiter.

Surgery offers the best results in cases of toxic goiter. A very large percentage of patients can be cured completely and permanently by thyroidectomy. On the other hand, cases clear up spontaneously and some are benefited by different forms of conservative treatment. Subtotal thyroidectomy cures about 70 per cent of cases of exophthalmic goiter and improves many others with very slight risk from the operation.

Group 4.—Thyroiditis does not occur often, but when it does it may present an interesting picture. The onset is usually gradual in an apparently otherwise normal gland, although sometimes it occurs in a gland in which there had been adenoma and colloid enlargements for some time. At the beginning the inflammation involves the entire gland. There is apt to be a complaint of pain and soreness and much tenderness on touching the gland which usually is not large, but the enlargement is general. The condition may go on to suppuration. The function of the thyroid may be disturbed by the inflammation. At first there may be nervousness, tremor, and loss of weight, and other suggestions of hyperthyroidism, but as the process continues the thyroid tissue is gradually destroyed and there are definite signs of hypothyroidism. If there is evidence of suppuration I believe that it is best to open into the softened area and drain. As a general rule when the inflammation involves the entire gland I do not believe that it is a good policy to operate. The operation is difficult due to the fact that there are firm adhesions between the entire surface of the gland and the surrounding structures and, furthermore, it is difficult to determine what gland tissue can best be saved. Normal thyroid function is more apt to follow conservative treatment than thyroidectomy.

Group 5.—Malignant tumors of the thyroid fortunately are rare. Sarcoma is almost never seen and carcinoma is much less than 1 per cent. Carcinoma of the thyroid, which can be diagnosed as such from its hardness and attachment to the surrounding tissues, may be considered inoperable. Even the cases of carcinoma operated on early are prone to recur and in a comparatively short time. It is to be hoped

that with the development of the treatment of malignancy by radium something can be offered these patients.

These questions are often asked by patients, "What will happen if the goiter is not removed?" or "Is it necessary to have this goiter removed?" They often ask whether the goiter will ever become malignant, whether it will continue to increase in size, produce nervousness, or prominence of the eyes. It seems to me that it is fair to the patients to tell them that they need have little fear of malignancy, but if they notice the adenoma growing harder or if there is any other change in them after a long quiescent period the tumor should be removed. In several patients on whom I have operated for malignant enlargements of the thyroid the enlargements had been noticed for twenty years or more, and yet in nearly every instance the patient came for treatment because there had been some recent change. At the time treatment is instituted for carcinoma it is almost hopeless.

Often ordinary goiters develop to a certain size and then remain quiescent for years. Sometimes in women at menopause the enlargement takes on new life and grows larger. It is also at this time that the type of toxic goiter, adenoma with hyperthyroidism, develops. The patient with a simple goiter may be assured that there is very slight chance that prominent eyes will develop, although after some years she may become nervous and have the other symptoms of a toxic goiter.

All things considered, the adenomas should be removed. It is certain that no other treatment will cause them to disappear, although it is equally certain that some persons may live to advanced age with goiter. If the goiter is a diffuse enlargement made up more of colloid than adenoma I believe there is a possibility that it will reduce in size and disappear.

CONCLUSIONS

Deficiency in thyroid function is manifested by a definite clinical syndrome. In most instances in adults these symptoms disappear following the administration of the active principle of the thyroid gland. In cretins without thyroid function at any time the amount of change that can be produced by giving thyroid is limited.

Disturbances in the parathyroid function result in a definite clinical syndrome. The symptoms in these cases apparently can nearly always be controlled by the administration of calcium lactate.

The adolescent goiter is a physiologic enlargement of the thyroid and should not be mistaken for hyperthyroidism. Studies in metabolism will often differentiate the two.

Thyroid enlargements producing mechanical interferences and those resulting in toxemia are best treated by surgical means.

Malignant enlargement if seen early should be operated on, although very little will be accomplished by attempting to remove the tumor if it is fixed to the surrounding structures.

MALIGNANT TUMORS OF THE THYROID*

PART II

PATHOLOGIC CLASSIFICATION AND DIAGNOSIS

LOUIS B. WILSON

General considerations.—Thyroid enlargements aside from hyperemia and inflammatory deposits vary so much in structure and present so little apparent relationship between their structure and the associated symptoms that diagnosis and classification are always extremely difficult. Perhaps for a clearer understanding we may lay aside for the moment our previously conceived ideas, our theories with regard to origin, and our impressions derived from exceptional or limited observations, and attempt first to blaze out certain broad general conceptions of the group.

Speaking from an experience gained in the pathologic study of about 14,000 human thyroids it seems to me that the following general conceptions may be formulated: Aside from hyperemia and inflammatory deposits, thyroid enlargements, as met with at operation and necropsy, are directly due either to storage of secretion or proliferation of tissue, or to both. If due to storage of secretion, they are colloid goiters. If due to diffuse proliferation (hyperplasia) of normal adult tissue which hyperfunctions, they are exophthalmic goiters. If due to circumscribed proliferation of (usually embryonal) parenchymatous tissue, they are adenomas. If these adenomas remain perfectly encapsulated and if they cease to proliferate and gradually degenerate they are "benign," in the sense that they do not invade surrounding structures and do not metastasize. They may, however, cause untoward local symptoms from pressure and they may be associated with a symptom syndrome, the chief characteristic of which is usually a slowly developing hypermetabolism with cardiac disturbances, but rarely with exophthalmos, a syndrome which H. S. Plummer designates "toxic nonexophthalmic goiter" or "toxic adenoma."

* Part I appears in the 1920 Collected Papers and the entire article is published in the *Annals of Surgery*, 1921, lxxiv, 129-184.

If adenomas continue to proliferate rather than to degenerate they may penetrate their capsule, invade the other portions of the gland or surrounding structures and metastasize, ultimately causing the death of the patient by destruction of either local or distant organs. These proliferating adenomas (the "wucherende Struma" of Langhans) thus may or may not be malignant and histologically it is almost impossible to differentiate the two. Broadly speaking, the only reliable marks of distinction are the details which indicate the predominance of one or the other of the two processes, namely, proliferation and degeneration. Again, broadly speaking, it follows from this, that any sizable adenoma of the thyroid composed of embryonal tissue in a person of cancer age which histologically shows that it is in active proliferation is potentially malignant even though it is still contained entirely within its capsule. This consideration, based on data supplied by a competent pathologist, should guide the surgeon at the time of operation in the extent of his operative procedures.

Neoplasms of the thyroid composed of adult parenchymatous cells, if encapsulated, always suggest having been derived from embryonal tissue during postnatal life, though by no means can this always be proved. Langhans considers them late stages of "wucherende Struma." Such encapsulated masses of large adult parenchymatous cells, while frequently arranged in acini resembling those of the normal thyroid, are more frequently the subject of extensive degeneration. And such degeneration may be sufficiently extensive to produce sloughing or broken-down areas. The epithelial cells adjacent thereto are large, often with hydropic cytoplasm and relatively small nuclei. The parenchyma is not infrequently markedly papilliferous. Such adenomas composed of epithelium, apparently adult in all respects, are associated with clinical conditions parallel with those mentioned as coincident with adenomas of embryonal type. They may cause only local pressure symptoms, they may be associated with the syndrome of toxic adenoma (Plummer), or they may invade surrounding structures and metastasize to distant organs, thus placing them in the class of malignant neoplasms. They are undoubtedly the origin of that group of malignant tumors usually designated adenocarcinomas.

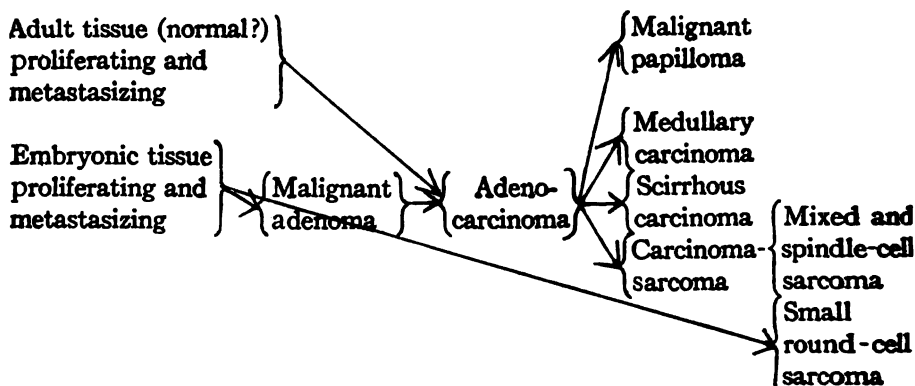
Occasionally there is met with an aberrant diffuse proliferation of parenchyma of the thyroid with little or no evidence of the formation of normal secretion or of the storage of colloid and without evidence of encapsulation except the normal capsule of the entire lobe. It is be-

lieved that such tumors may exist without causing other than local symptoms and these but slight. I have seen not more than ten or fifteen of these in my entire experience. On the other hand, solid homogeneous nonfunctioning aberrant proliferations of the thyroid are almost always neoplasms which invade surrounding structures and metastasize to distant organs. While in one sense these are adenocarcinomas, for the sake of clearness let us leave out of account their suggestion of nodular encapsulated neoplasms and refer to them simply as carcinomas of the thyroid.

All other tumors of the thyroid associated with symptoms of malignancy are usually described as sarcomas. Besides their connective-tissue elements in which any form of sarcoma cell may be the dominant one, although it is most frequently the spindle-cell type, there are also almost invariably present large or small groups of parenchymatous cells which show that they are also proliferating. Whether or not the neoplastic process started with the parenchymal elements which were later destroyed by a secondary proliferation of the connective-tissue elements, or whether the process was from the beginning a proliferation of the connective-tissue elements with only secondary stimulation of the parenchymatous cells as they were gradually squeezed out, it is impossible to say. There is usually a history of recent rapid development, and the prognosis of the early demise of the patient must be made. We must continue to call these tumors sarcomas whatever may be our hypothesis with regard to their epithelial or mixed origin.

MORPHOLOGIC RELATIONSHIPS

In studying the pathologic diagnosis of malignant tumors of the thyroid some assistance may be obtained by following, in reverse order, the diagram presented herewith:



This diagram is an attempt to express what appear to be the gradations from tumors of one type of tissue to those of other types which have been found in the series of malignant tumors of the thyroid herewith reported. It is possible that other types exist, but they have not come under my observation. Thus, no hard-and-fast line of differentiation can be drawn between tumors composed of embryonic tissue (fetal adenoma, wucherende Struma, Langhans) which is proliferating and metastasizing and those types of adenomas composed of cells approaching the adult type, but arranged in fairly normal acini or in bands. Nor is it possible to draw hard-and-fast lines between tumors of this latter type of tissue and tumors composed of cells of more or less adult type forming tissue masses, most of which are composed of cells rather densely packed together and showing only here and there enough evidence of their acinar arrangement to indicate their thyroid gland origin, and hence called adenocarcinomas. Adenocarcinomas, in turn, are subject to at least four types of variation, which in their extreme development are readily recognized, but which grade into ordinary adenocarcinoma of the solid type and even into each other in all degrees of variation. As a rule it is much easier to determine histologically the malignancy of adenocarcinomas, including the four principal variations, papilloma, medullary carcinoma, scirrhus carcinoma, and carcinosarcoma, than it is to determine histologically the malignancy of either adult or embryonic adenomas.

ILLUSTRATIVE CASES

The following illustrations show the principal tumor types in inverse order of the diagram, beginning with those which are most easily recognized. The illustrations are presented in the hope that they may assist other observers in making diagnoses. Only enough of the clinical history is presented to serve as a check on the pathologic diagnosis.

MALIGNANT PAPILLOMA

Case 1 (A53517). A man, aged sixty-five years, had had goiter two years before operation. The left lobe, isthmus, and lower pole of the right lobe were extirpated. Sixty grams of tissue were removed. Recurrence followed in eight months, and the patient died three years after the operation.

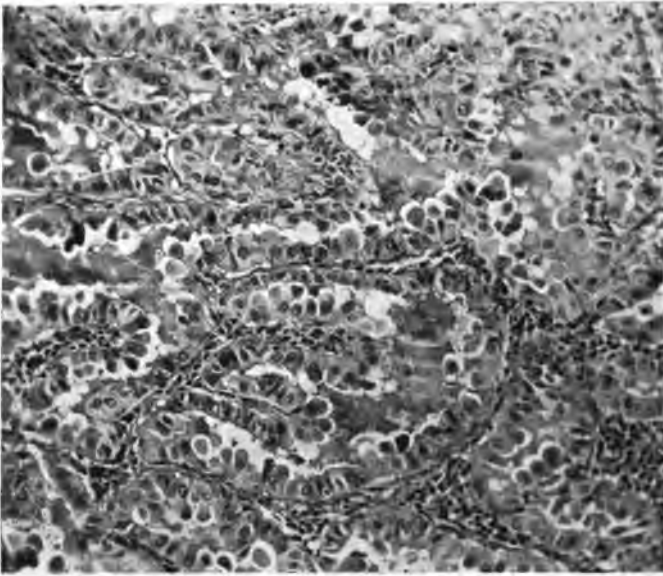


FIG. 145 (Case A53517).—The papillæ bear large functioning cells (see colloid and surrounding clear spaces), with sharply staining nuclei and mitotic figures. Malignant papilloma. $\times 100$.

MALIGNANT PAPILLOMA

Case 2 (A85166). A man, aged fifty-one years, had had goiter for eighteen months; rapidly growing for five months. At operation a malignant papilloma of the right lobe, involving the trachea and muscles, was found. One hundred thirty-two grams of tissue were removed. There was a rapid recurrence of the tumor and the patient died two and one-half months after the operation.

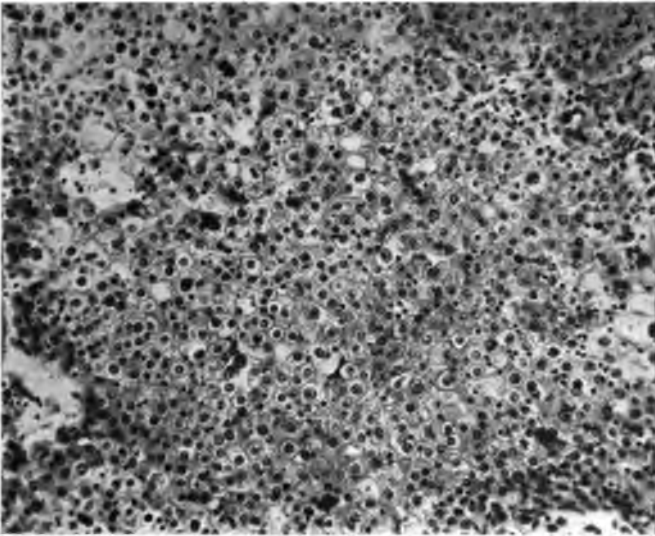


FIG. 146 (Case A85166).—A section through the base of papillæ which resemble those shown in Figure 145. Large and small epithelial cells, showing evidence of rapid proliferation. Malignant papilloma. $\times 100$.

NONMALIGNANT PAPILLOMA

Case 3 (A39582). A woman, aged thirty-seven years, had had goiter for two years. The left lobe and isthmus were extirpated. The growth was a papilloma. Twenty-eight grams of tissue were removed. The patient's recovery was uneventful, and there was no recurrence during a period of ten years after the operation.

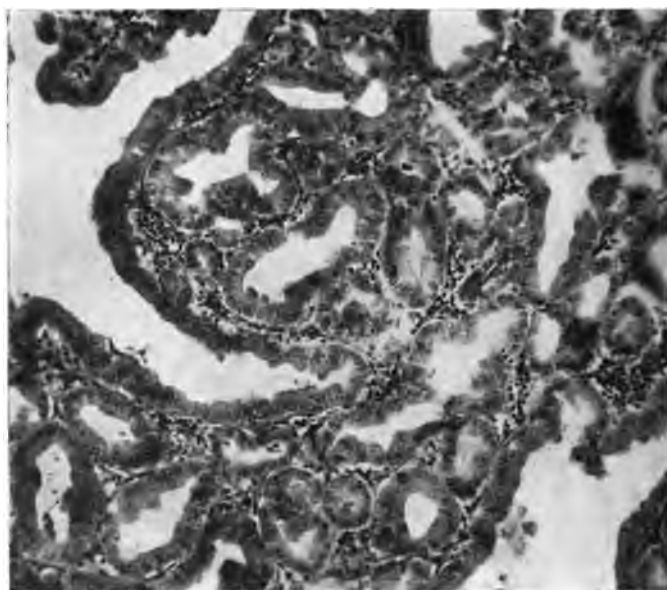


FIG. 147 (Case A39582).—High columnar epithelium with small nuclei; no mitosis. Non-malignant papilloma. $\times 100$.

NONMALIGNANT PAPILLOMA

Case 4 (A95417). A woman, aged twenty-three years, had had goiter for seven years previous to operation. Cysts were enucleated from the right lobe and isthmus. Forty-five grams of tissue were removed. There was no recurrence during seven years after operation.

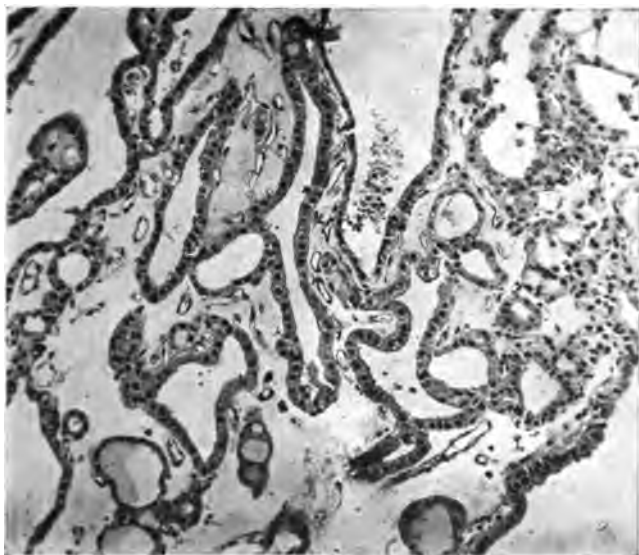


FIG. 148 (Case A95417).—Note clear hyaline centers of papillæ, small epithelial cells with shrunken nuclei without mitosis. Nonmalignant papilloma. $\times 100$.

ADENOPAPILLOMA

Case 5 (A47855). A man, aged forty-nine years, had had goiter for five years with rapid growth for one year. The right lobe and isthmus were extirpated for impending suffocation. Four hundred twenty-five grams of tissue were removed. Recurrence followed within one year; there were nodules in the scar, and hemorrhages apparently from the larynx. Death occurred eighteen months after the operation.

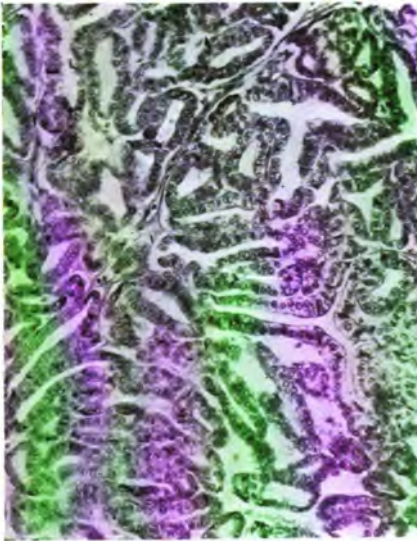


FIG. 149 (Case A47855).—Rapidly proliferating papilloma. $\times 100$.

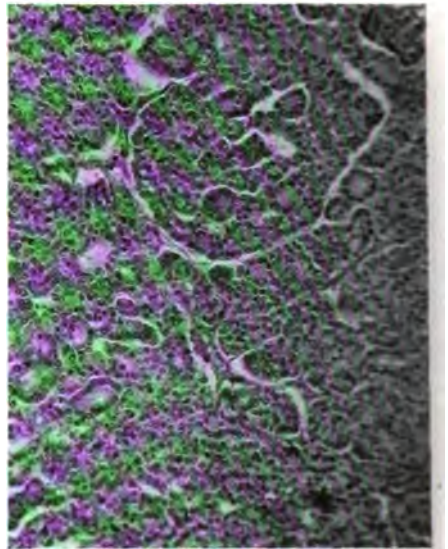


FIG. 150 (Case A47855).—Adenomatous areas showing only slight tendency to papillae formation. Small embryonic cells with relatively large nuclei. Adenopapilloma, malignant. $\times 100$.

ADENOPAPILLOMA (MALIGNANT)

Case 6 (A94082). A woman, aged forty years, had had goiter for sixteen years with accelerated growth for two years. A dense calcareous goiter was adherent to the trachea, and all the anterior muscles were involved. It was impossible to remove the entire growth. Fifteen grams of tissue were removed. Roentgen-ray treatments were given for four months, during which time the growth largely disappeared; it recurred three years after operation. The patient is alive and not suffering serious inconvenience six years after operation.

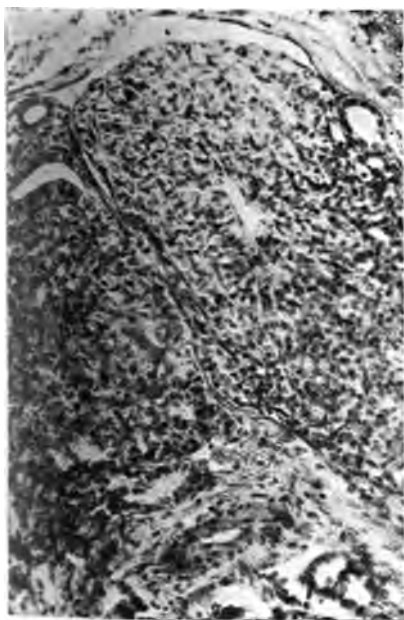


FIG. 151 (Case A94082).—A section at the base of the papillomatous area. The epithelial cells are evidently proliferating. $\times 100$.



FIG. 152 (Case A94082).—Adenomatous area; small partly differentiated cells with relatively large nuclei separated into short irregular twisted cordons by thin-walled flat capillaries. Adenopapilloma, malignant. $\times 100$.

MEDULLARY CARCINOMA

Case 7 (A16767). A man, aged forty-eight years, had had goiter for five years; slowly growing for the last few months. The right lobe and isthmus were extirpated. Four hundred grams of tissue were removed. The patient was reexamined twenty-two months later, and then had obstruction and dyspnea. A hard, nodular tumor 5 by 5 inches was found in the right thyroid region; it had grown rapidly for the last few months. The patient died two years after operation.

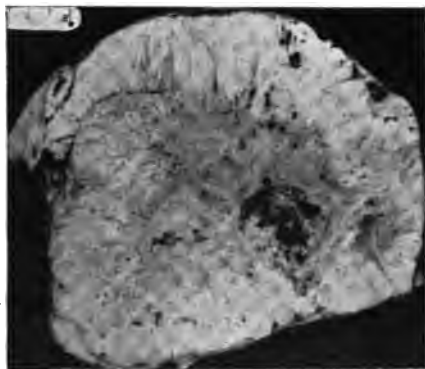


FIG. 153 (Case A16767).—A gross section through the tumor showing fibrous scar-like center with adenomatous subcapsular portion, and fibrous lines radiating from the center to the capsule. This arrangement is typical of the proliferating embryonic adenomas and suggests the origin of this medullary carcinoma from such a tumor. Medullary carcinoma.



FIG. 154 (Case A16767).—A section from the fibrous area showing large epithelial cells in small acini, degenerating. $\times 100$.

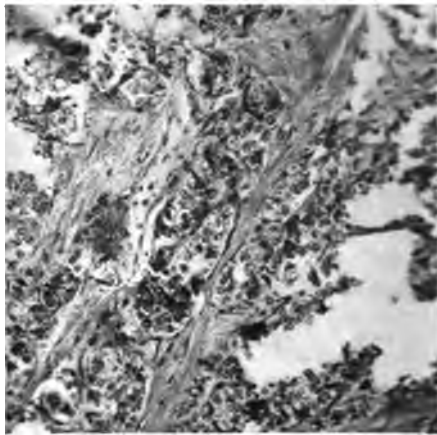


FIG. 155 (Case A16767).—A section through the soft portion of the tumor. Portions of three large acini shown densely crowded with medium-sized epithelial cells which are breaking down; one area of colloid. $\times 100$.

MEDULLARY CARCINOMA

Case 8 (A44143). A man, aged forty-one years, had had a hard goiter for twenty years; it had enlarged rapidly during the last year. An adenoma of the isthmus, which invaded both lobes, penetrated at the base, and involved the muscles; the mediastinum was enucleated. Three hundred five grams of tissue were removed. One month after operation a rapidly growing tumor recurred. The patient died two months after the operation.

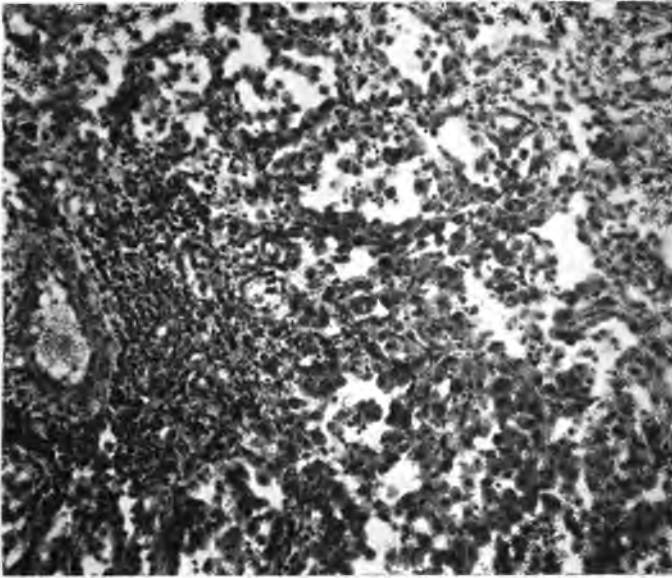


FIG. 156 (Case A44143).—A section through the soft portion of the tumor showing large proliferating and degenerating epithelial cells in loose acini. Medullary carcinoma. $\times 100$.

MEDULLARY CARCINOMA

Case 9 (A109792). A man, aged sixty-five years, had had goiter for twenty-two years; growing more rapidly for the past eight years. A clinical diagnosis was made of multiple adenomas, possibly malignant. The patient refused operation. He returned twenty-one months later, having used local applications. The tumor was slightly larger than before, inflamed, and more fixed. The pyramidal and median lobes were resected. Three hundred ninety-five grams of tissue were removed. One month later a recurring growth was removed by the Percy cautery. The cautery was used again in one month, followed by radium treatment. The patient died three months after the first operation.

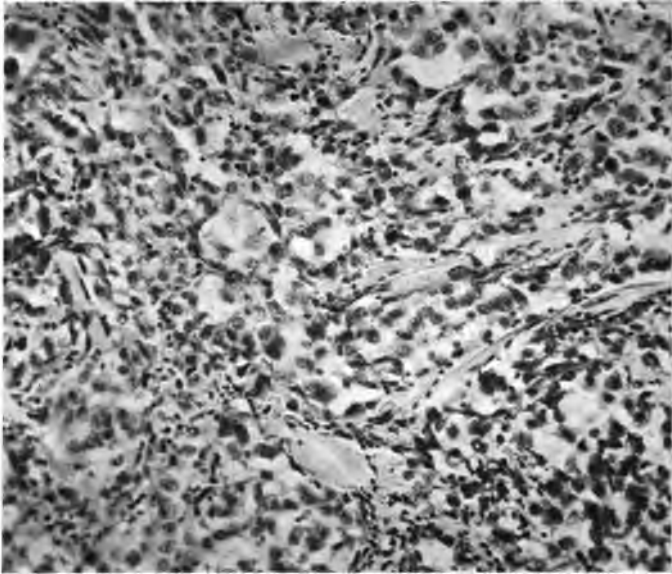


FIG. 157 (Case A109792).—Large epithelial cells evidently rapidly proliferating, some acinar arrangement. Medullary carcinoma. $\times 100$.

ADENOMEDULLARY CARCINOMA

Case 10 (A119660). A woman, aged forty-three years, had had goiter for fourteen years with accelerated growth for five years. An adenoma of the isthmus which invaded both lobes was removed. Two hundred forty grams of tissue were removed. The tumor recurred two and one-half years after the operation. The patient died three years after the operation with extensive metastasis in the lungs.



FIG. 158 (Case A119660).—A gross section through a portion of tumor showing typical proliferating adenoma arrangement. Adenomedullary carcinoma. $\times 100$.

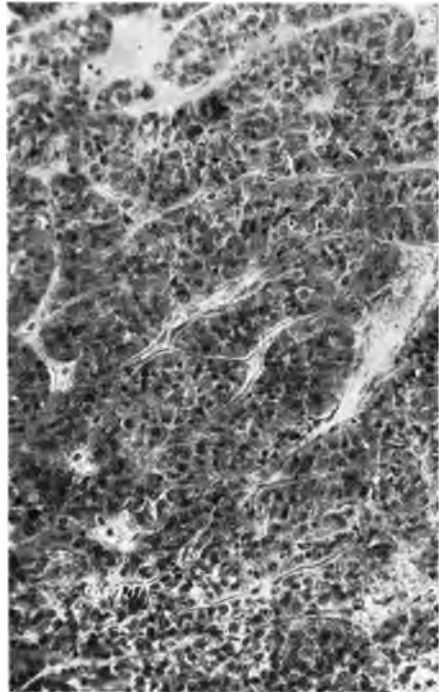


FIG. 159 (Case A119660).—A section through the softer portion of tumor showing large epithelial cells proliferating and degenerating lying in well-marked cords and follicles. The character of cells indicates the beginning medullary type. Arrangement shows plainly adenomatous origin. $\times 100$.

ADENOMEDULLARY CARCINOMA

Case 11 (A96681). A woman, aged thirty-four years, had had goiter for eight years. A partial thyroidectomy had been performed twice elsewhere during the last two years. No pathologic examination of the tissue removed at these operations had been made. There had been a recent rapid growth. All of the right lobe except the superior pole was removed. Seventy-two grams of tissue were removed. Three months later a rapidly recurring growth including tissue from behind the larynx was removed by excision and cautery, and a tracheotomy performed. Death occurred one month later. Extensive metastasis was found to the lungs, lymphatics, and left sternoclavicular articulation.

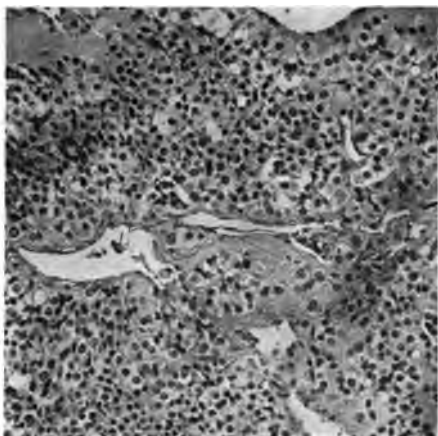


FIG. 160 (Case A96681).—A section through the more solid portion of the thyroid tumor. Large epithelial cells showing traces of alveolar arrangement. $\times 100$.

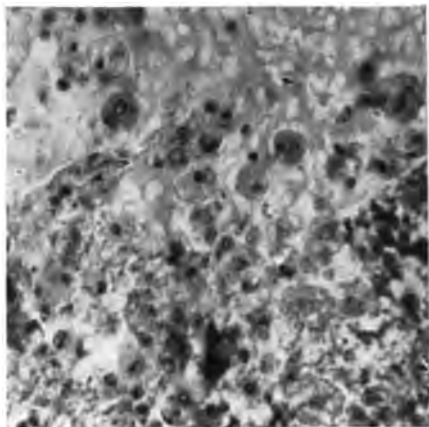


FIG. 161 (Case A96681).—A section through the soft portion of the recurring tumor showing a "medullary" type of cells. $\times 220$.

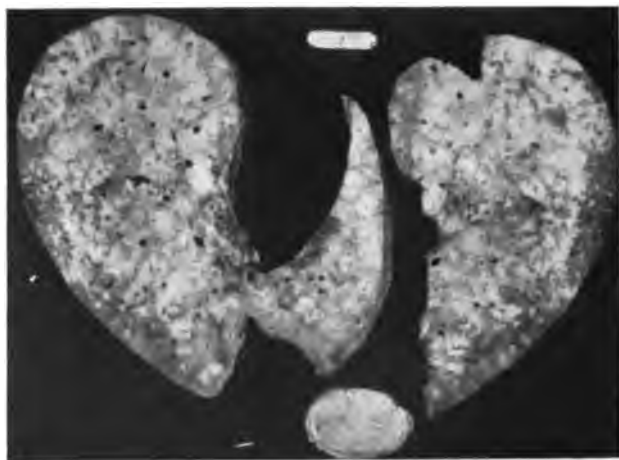


FIG. 162 (Case A96681).—A gross section through the lungs. Light areas show metastasis. Adenomedullary carcinoma.

SCIRRHOUS CARCINOMA

Case 12 (G6848). A man, aged forty-eight years, had noticed gradual trouble in the right side of his neck and in his tonsils for the past year. The right lobe of the thyroid, the sternomastoid, and omohyoid muscles, the internal jugular and the lymphatics on the right side were removed. One hundred grams of tissue were removed. Four years after the operation the patient wrote, "I think the operation could not have been better; neck has not swelled or bothered me since. Now have asthma more or less." The patient died five years after the operation with involvement of the lungs.

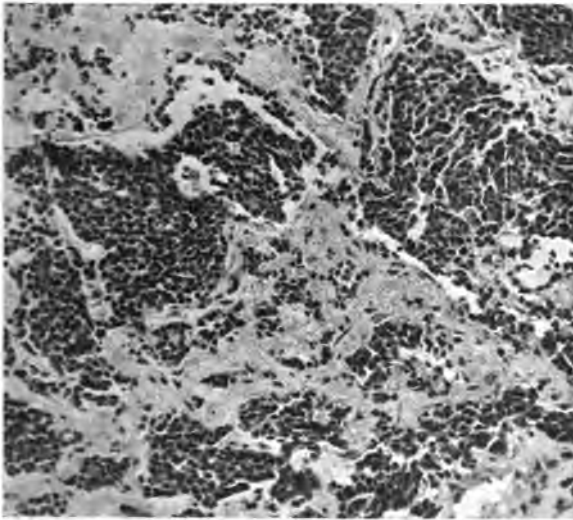


FIG. 163 (Case G6848).—A section through a hard portion of the tumor in the thyroid, showing epithelial cells much condensed by fibrous connective tissue. Scirrhous carcinoma. $\times 100$.

SCIRRHOUS CARCINOMA

Case 13 (A68082). A man, aged twenty-six years, had had a small tumor on the right side of his neck since childhood; it had enlarged in the past two years. Three years before it had been diagnosed goiter by his physician. He had been dyspneic during the past year. On exploration a large intrathoracic tumor was found which could not be removed and tracheotomy was performed. Twenty grams of tissue were removed for diagnosis. The patient died three days after the operation. Necropsy revealed a tumor involving the trachea, which was reduced to ribbon shape and extended into the mediastinum to the pericardium. The mediastinal glands were involved. There were numerous metastatic nodules in the liver and spleen.



FIG. 164 (Case A68082).—The trachea opened from behind, showing small carcinomatous nodules under the mucosa.

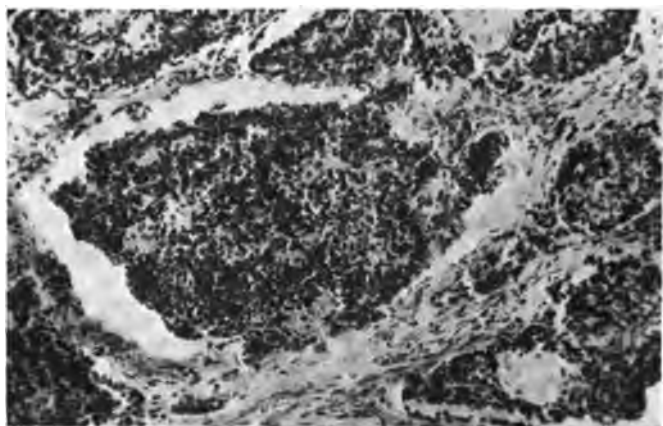


FIG. 165 (Case A68082).—Epithelial cells condensed by fibrous connective tissue. Scirrhous carcinoma. $\times 100$.

SCIRRHOUS ADENOCARCINOMA

Case 14 (A89086). A woman, aged thirty-four years, had had goiter for twenty years, with accelerated growth for five years, but no serious symptoms until seven months before. The left lobe of the thyroid was extirpated. Twenty-five grams of tissue were removed. The patient died nine months after the operation from recurrence.

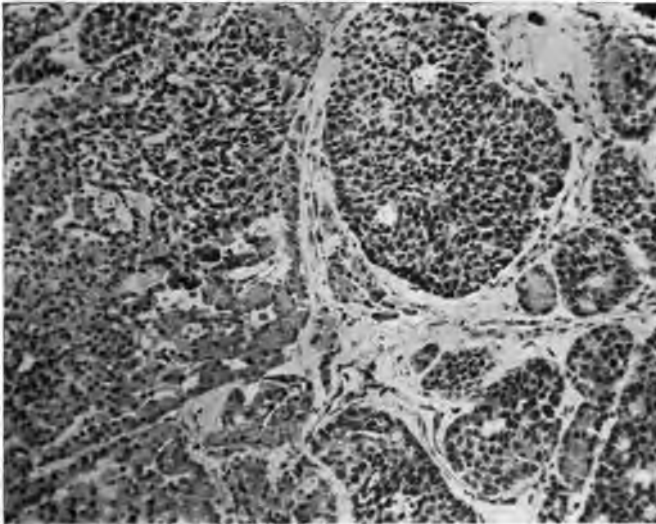


FIG. 166 (Case A89086).—Epithelial cells in crowded acini; nuclei though distorted resemble those in embryonic cells, suggesting derivation from proliferating embryonic adenoma. Scirrhous adenocarcinoma. $\times 100$.

MIXED-CELL SARCOMA

Case 15 (A19893). A woman, aged thirty-nine years, had had goiter for seven years, with rapid growth during the last six months. A firm, almost hard, spherical, movable enlargement was palpated in the right lobe of the thyroid. The tumor, which was about 7 cm. in diameter, was attached to the trachea and had infiltrated through the capsule. One hundred thirty-six grams of tissue were removed. Six centimeters of the right internal jugular were removed with the tumor. Death occurred six months after the operation.

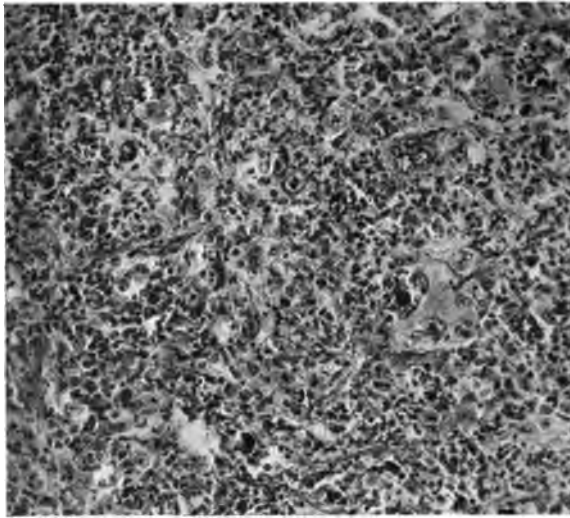


FIG. 167 (Case A19893).—Mixed, round, spindle-, and giant-cell sarcoma. $\times 100$.

SPINDLE-CELL SARCOMA

Case 16 (A59130). A man, aged fifty-six years, had had goiter for twelve years, with accelerated growth for about three years. The left lobe and isthmus were extirpated; the tumor was infiltrating the muscle. Two hundred twenty grams of tissue were removed. The patient died two months after the operation.



FIG. 168 (Case A59130).—A section through a gross specimen, showing solid and spongy areas.

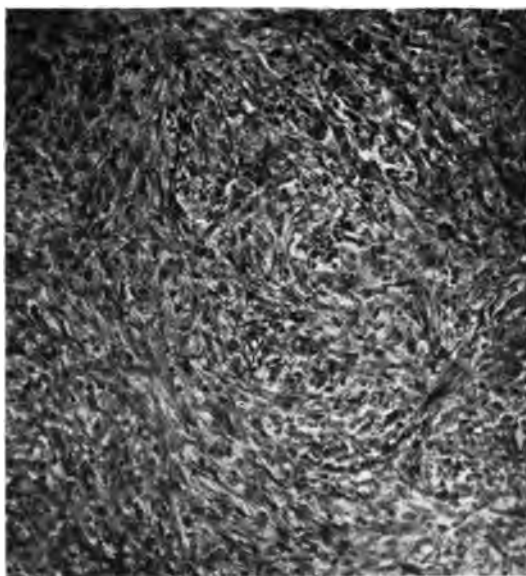


FIG. 169 (Case A59130).—A section through a solid area showing spindle-cell sarcoma with a few round cells. $\times 100$.

ALVEOLAR SARCOMA SUGGESTING EPITHELIAL RELATIONSHIP

Case 17 (A138004). A woman, aged sixty-four years, who did not give a history of previous goiter, had noted a rapid growth of the thyroid for three months. At exploratory operation a small piece of tissue was removed for diagnosis. Death occurred four months after the operation.

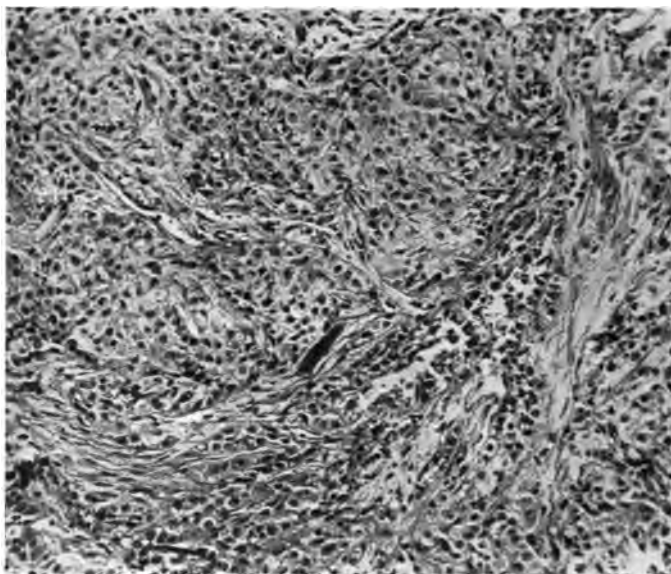


FIG. 170 (Case A138004).—Alveolar sarcoma. $\times 100$.

CARCINOMA SARCOMA

Case 18 (A163873). A woman, aged fifty-two years, had had goiter for thirty-seven years with accelerated growth for one year. A total thyroidectomy was performed for advanced malignant tumor, involving the right lobe of the thyroid. Two hundred ten grams of tissue were removed from the right lobe. The growth recurred nine months after the operation.

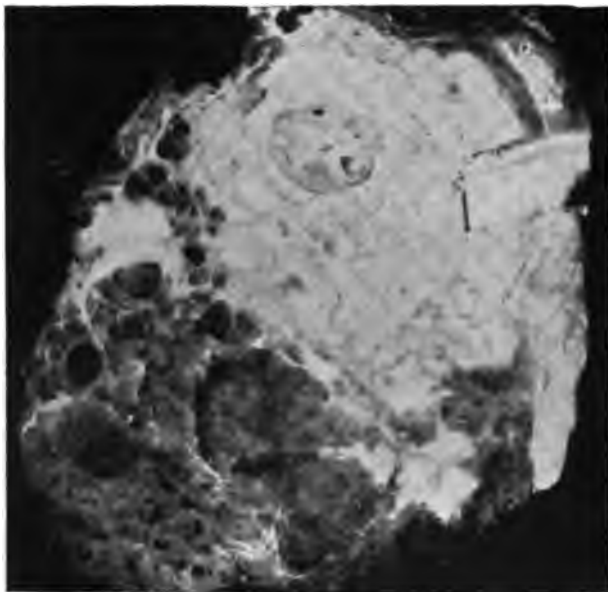


FIG. 171 (Case A163873).—A section through the gross specimen showing a tumor developing in the adenoma in the old colloid goiter.

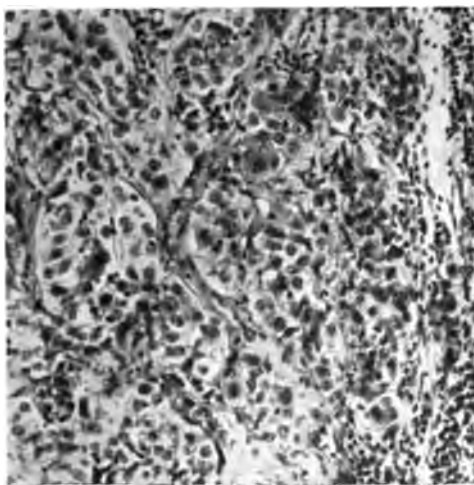


FIG. 172 (Case A163873).—A section through the portion of solid tumor near the capsule, showing proliferation of both epithelial and connective-tissue elements. $\times 100$.

CARCINOMA SARCOMA

Case 19 (A57935). A woman, aged sixty-three years, had had very hard deep-lying tumors in the right and left lobes of the thyroid for four years. The entire thyroid gland was extirpated. Two hundred grams of tissue were removed. The patient remained apparently well for six years, then died within nine months of rapid recurrence with extensive metastasis.

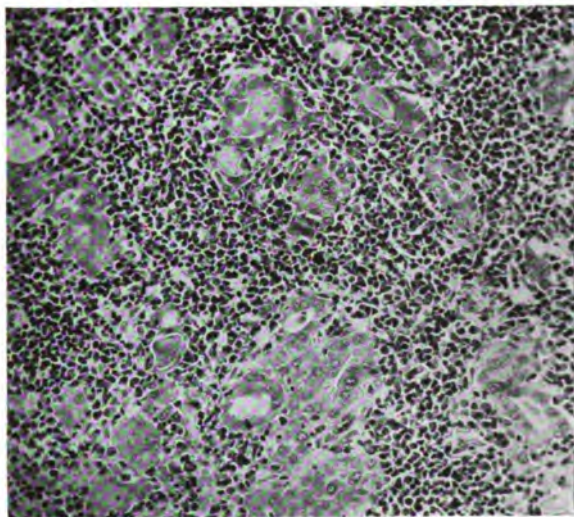


FIG. 173 (Case A57935).—A section through the edge of the tumor, showing proliferated epithelial cells which are now degenerating, and proliferation of connective-tissue cells between the acini. Carcinoma sarcoma. $\times 100$.

ROUND- AND GIANT-CELL ADENOSARCOMA

Case 20 (A32772). A man, aged seventy years, had had goiter for sixteen years which had gradually enlarged for eleven years, remained stationary for three years, and then gradually enlarged for two years. A hard nodular goiter was enucleated from the left side. Two hundred twenty grams of tissue were removed. The growth recurred in two months and death occurred in four months.

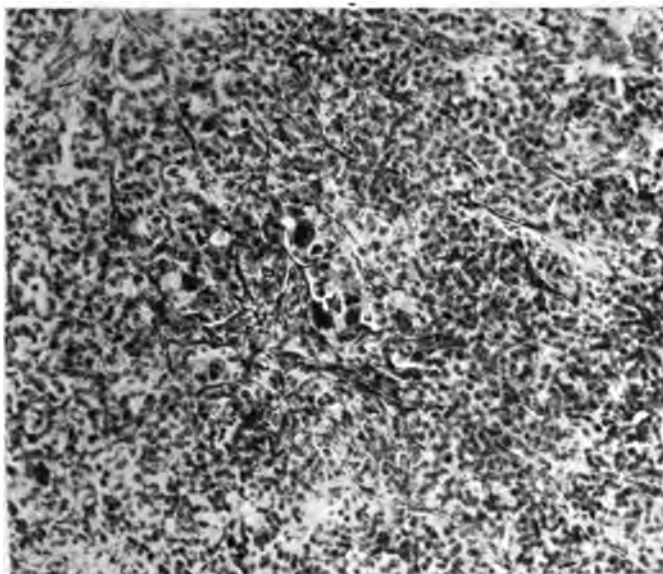


FIG. 174 (Case A32772).—Sarcoma composed of small round and giant cells; small round cells still showing marked evidence by their grouping of their origin as embryonic adenomas. $\times 100$.

SMALL ROUND-CELL SARCOMA

Case 21 (A182791). A woman, aged fifty-nine years, had had goiter for one year, with accelerated growth for two months. The entire right lobe and isthmus and all of the left lobe except a piece of gland half the size of a normal lobe which was left at the lower pole were removed. One hundred sixty-five grams of tissue were removed from the right lobe; seventy grams were removed from the left. The patient was reexamined four months after the operation. She was dyspneic on exertion, worse during the last two months. Death occurred two years after the operation from "trouble with lungs"; no necropsy.

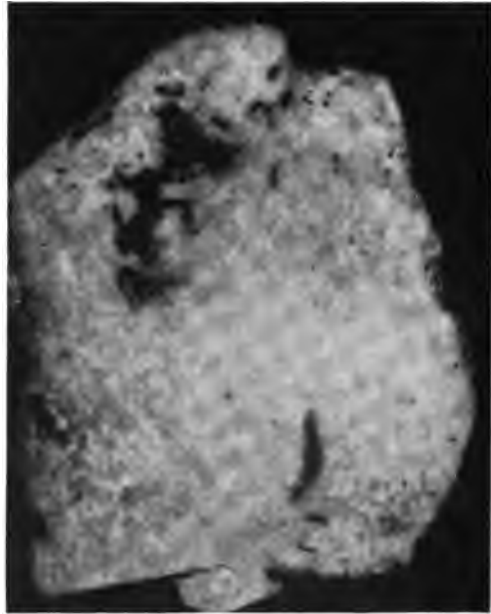


FIG. 175 (Case A182791).—A section through the more solid portion of the tumor, showing small areas of colloid thyroid (dark) here and there in the tumor.

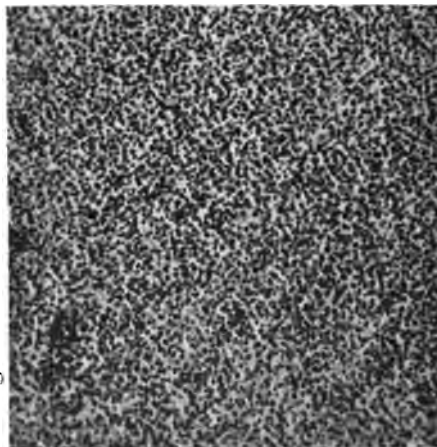


FIG. 176 (Case A182791).—Small round-cell sarcoma. In some areas cell grouping suggests that in embryonic adenomas. $\times 100$.

SMALL ROUND-CELL SARCOMA

Case 22 (A30889). A woman, aged fifty-two years, had had a slowly growing goiter for one year. The entire gland was extirpated. Eighty-six grams of tissue were removed. The growth recurred two months later and was treated by roentgen ray. There was some evidence of metastasis five and one-half years after operation. Death occurred six years after operation.

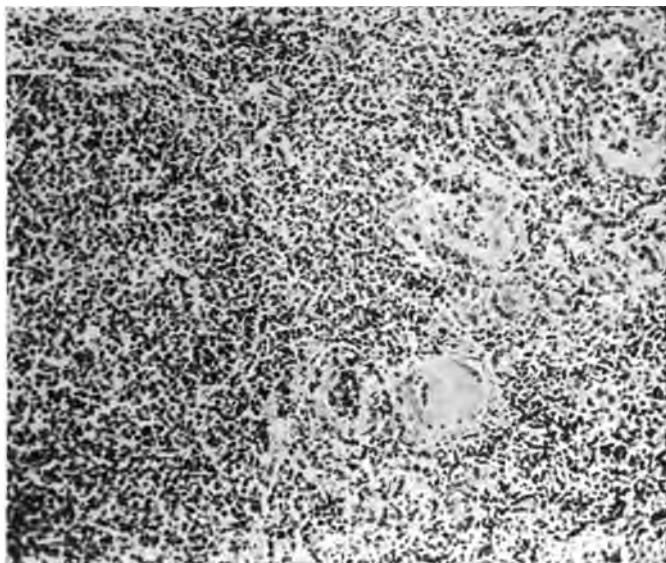


FIG. 177 (Case A30889).—Small round cells here and there in groups suggesting partially differentiated embryonic adenomatous tissue. Small round-cell sarcoma. $\times 100$.

ADENOCARCINOMA

Case 23 (P5459). A woman, aged sixty-six years, had had goiter for thirty years, rapidly growing for four months. She was dyspneic; had mucus in the trachea that was hard to get up. A complete thyroidectomy was performed. Three hundred eighteen grams of tissue were removed. Death occurred one year after the operation.

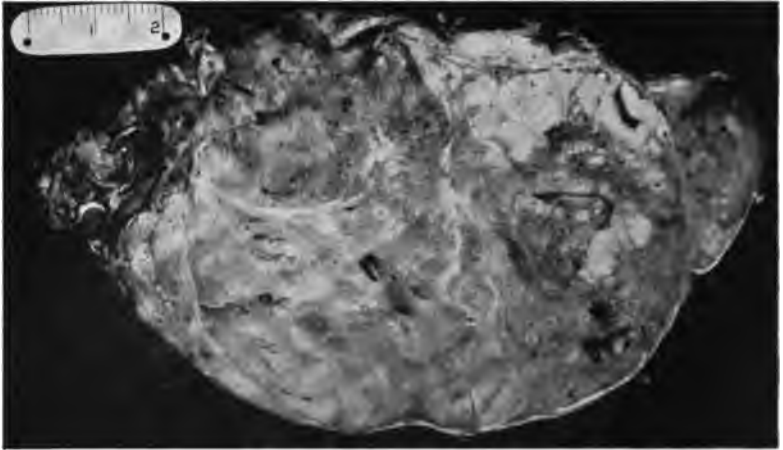


FIG. 178 (Case P5459).—A section through the gross specimen, showing encapsulated mass of tumor tissue (light) advancing into colloid areas (dark).

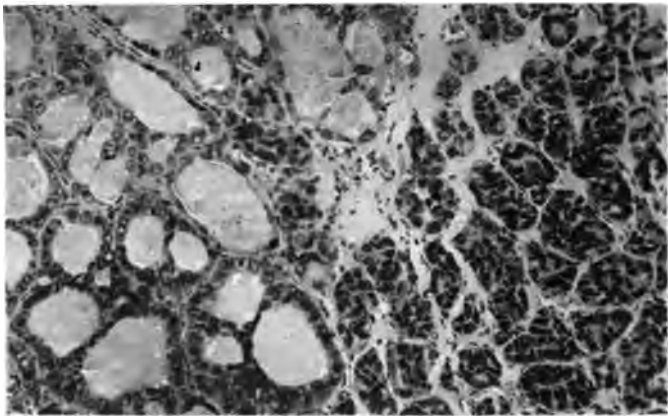


FIG. 179 (Case P5459).—Edge of the tumor area showing adenocarcinoma in colloid adenoma. $\times 100$.

ADENOCARCINOMA

Case 24 (A26084). A woman, aged thirty-eight years, had had a gradually growing goiter for four years. An adenoma was enucleated from the left lobe of the thyroid. Forty-eight grams of tissue were removed. Six years after the operation a rapidly growing recurrent tumor developed. Death occurred six and one-half years after operation from involvement of the larynx and trachea.

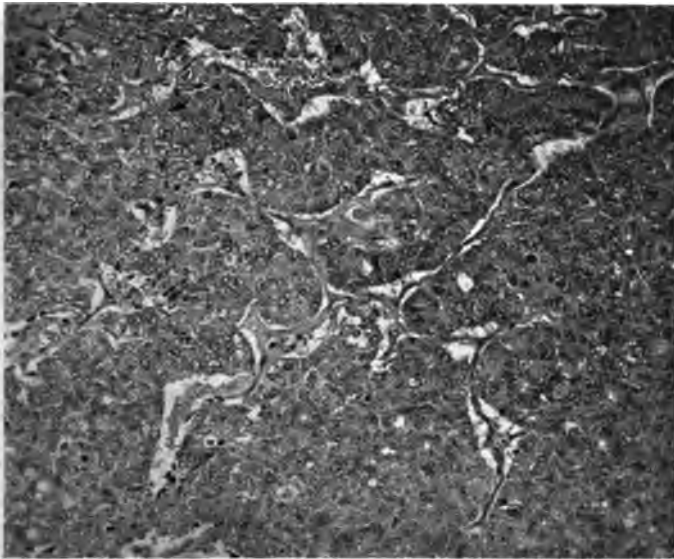


FIG. 180 (Case A26084).—Carcinoma composed of adult epithelial cells in some places arranged in irregular whorls like those of proliferating embryonic adenomas. $\times 100$.

ADENOCARCINOMA

Case 25 (A91931). A man, aged fifty-seven years, had had goiter for eighteen months. Thyroidectomy was performed; the trachea was freed, and a portion of the right lobe removed. Twenty grams of tissue were removed. The tumor which originated in and involved mainly the right lobe, had perforated the muscles and involved the sternomastoid muscle on the right side. Roentgen-ray treatment was given for three months, then the cancer eroded through the skin. The patient went to a "plaster specialist." Several severe hemorrhages occurred after the "plaster treatment." The patient died one year after operation.

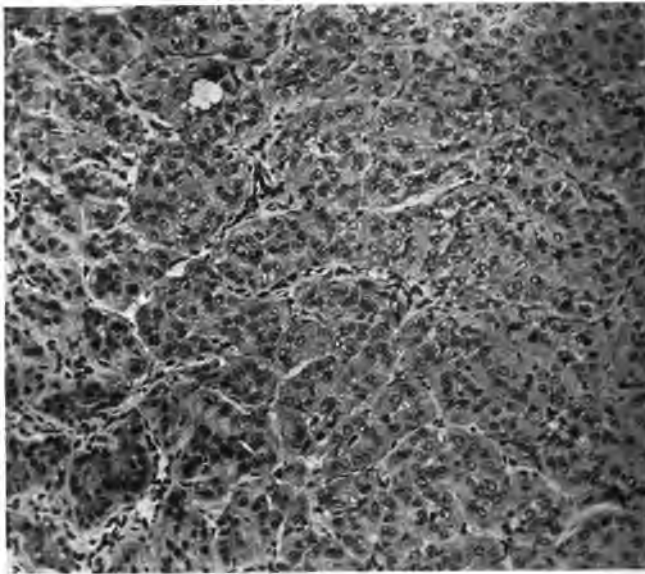


FIG. 181 (Case A91931).—Adenocarcinoma composed of adult epithelial cells arranged everywhere in masses typical of embryonic proliferating adenomas. $\times 100$.

MALIGNANT ADENOMA

Case 26 (A23842). A woman, aged twenty-seven years, had had goiter for ten years; it had grown gradually until about two months before, when it began to increase more rapidly. A nodular tumor of the right lobe was extirpated. One hundred ninety grams of tissue were removed. The patient returned for examination four years after operation with recurrence of a tumor in the right lobe. The entire right lobe of the thyroid, which was fixed to the trachea and cricoid cartilage and involved the larynx, was removed. One hundred grams of tissue were removed. Two and one-half years after the second operation the patient reported that the gland was enlarging slowly; she was growing weaker and showing some cachexia. Death occurred eight years after the first operation from tracheal involvement and probably metastasis to the lungs.



FIG. 182 (Case A23842).—A section through a gross specimen showing the ordinary type of proliferating adenoma with gland tissue in the center of the nodule replaced by connective tissue.

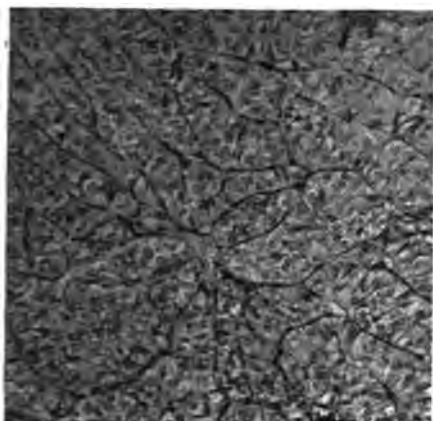


FIG. 183 (Case A23842).—A section through the solid area of a tumor near the capsule, showing adult epithelial cells in lobules and long narrow bands corresponding to Langhans' description; mitosis in cells. $\times 100$.

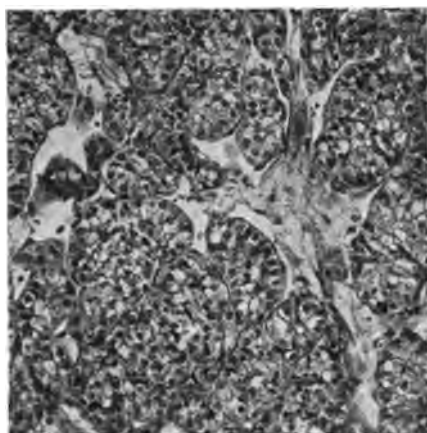


FIG. 184 (Case A23842).—A section through a looser area. Lobules arranged in short whorls; cells show colloid, although definite acini are absent. $\times 100$.

PROLIFERATING EMBRYONIC (FETAL) ADENOMA, MALIGNANT

Case 27 (A164145). A man, aged fifty-one years, had had goiter for seventeen years with accelerated growth for five years. There was slight hyperthyroidism. An adenoma was enucleated from the right lobe of the thyroid. The gland was densely fixed posteriorly. Four hundred eighty grams of tissue were removed. Roentgen ray and radium treatment were given for one month following the operation. Five months after the operation examination revealed considerable enlargement of the right lobe. The patient was alive and well when last heard from two years after the operation.

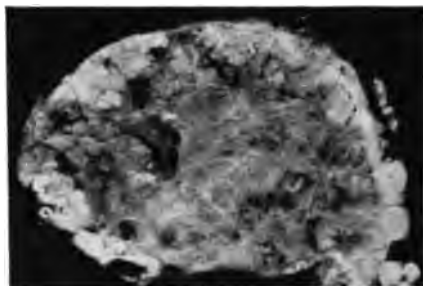


FIG. 185 (Case A164145).—A section through the gross specimen showing extensive hyaline and fibrous degeneration. Compare this with Figures 182, 188, and 190.

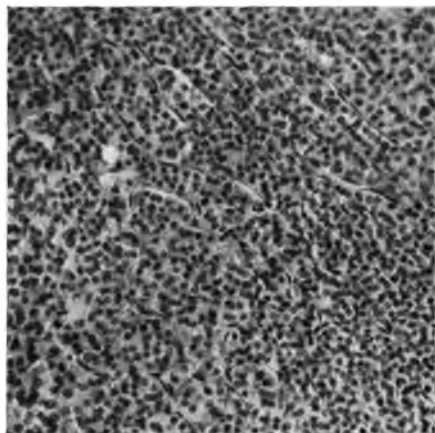


FIG. 186 (Case A164145).—A section through the dense portion of the adenoma immediately under the capsule. Note small embryonic cells arranged in lobules and bands with a very small amount of stroma (thin-walled blood vessels) between. $\times 100$.

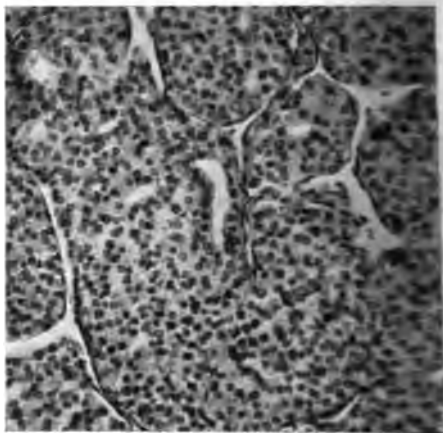


FIG. 187 (Case A164145).—A section from an area farther from the capsule than that shown in Figure 186. The embryonic cells are larger and in larger lobules, marked off by cleft-formed blood vessels. $\times 100$.

PROLIFERATING EMBRYONIC (FETAL) ADENOMA, MALIGNANT

Case 28 (A155669). A man, aged forty-five years, had had goiter for twenty years with accelerated growth for two years. Two partial thyroidectomies had been performed elsewhere, twelve and seven years before respectively. No data were obtainable concerning the character of the removed tissue. A partial thyroidectomy was performed. Forty-five grams of tissue were removed. Four months later the home physician reported that the patient was in good health and working every day. One year after the operation serious pressure on the trachea was reported. Death occurred one year and four months after the operation, following tracheotomy for pressure made by a large tumor of the thyroid. No necropsy was made and no data were obtainable concerning the histology of the tumor or of possible metastasis.



FIG. 188 (Case A155669).—A section through the small adenoma removed at the third operation (the first in the Mayo Clinic). The entire nodule made up of actively growing tissue.

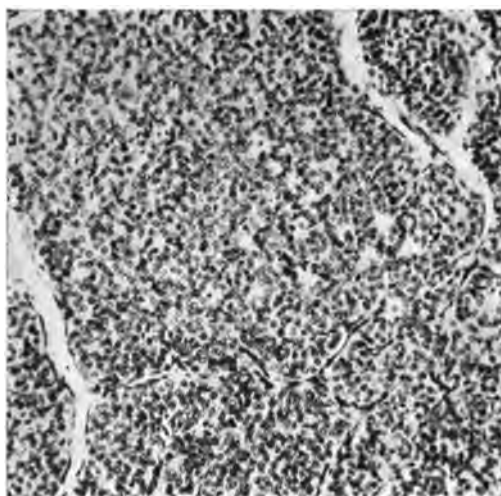


FIG. 189 (Case A155669).—A section through the tumor showing proliferating embryonic epithelium in some areas arranged in lobules. $\times 100$.

PROLIFERATING EMBRYONIC (FETAL) ADENOMA

Case 29 (A91228). A man, aged twenty-six years, had had a slow growing goiter for three years. Thyroidectomy was performed; a substernal goiter was partially removed. Five hundred fifty grams of tissue were removed. The patient was reexamined one year later. Goiter had recurred seven months after the first operation, producing marked obstruction during the last three months. A second operation was performed one year after the first; death occurred one year and eight months later.

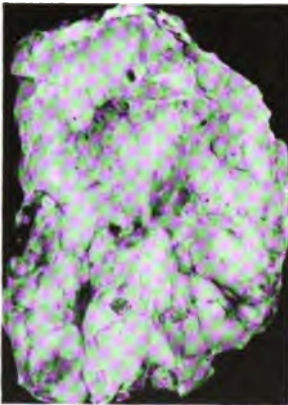


FIG. 190 (Case A91228).—A section through the gross specimen. Almost the entire tumor is composed of rapidly growing tissue.

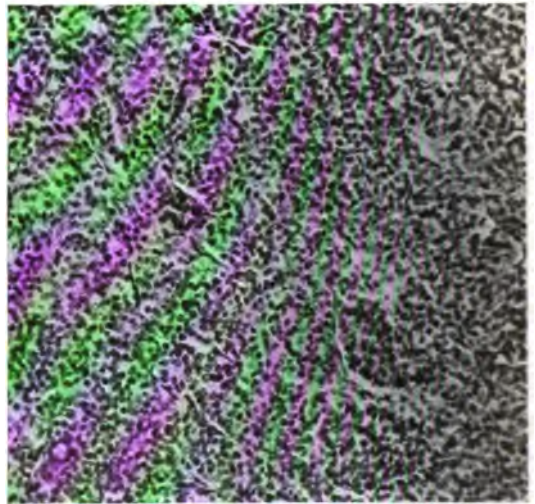


FIG. 191 (Case A91228).—A section through the tumor near the capsule; embryonic cells are arranged in feebly demarked lobules. $\times 100$.

PROLIFERATING EMBRYONIC (FETAL) ADENOMA, FIBROUS DEGENERATION

Case 30 (A23200). A woman, aged thirty-seven years, had had goiter for twenty-nine years. A hard tumor of the right lobe of the thyroid was enucleated. The center of the tumor was broken down. One hundred eight grams of tissue were removed. The patient was reexamined seven years after the operation. The left lobe of thyroid was slightly enlarged. There were no symptoms. The patient was in excellent health eleven years after the operation.

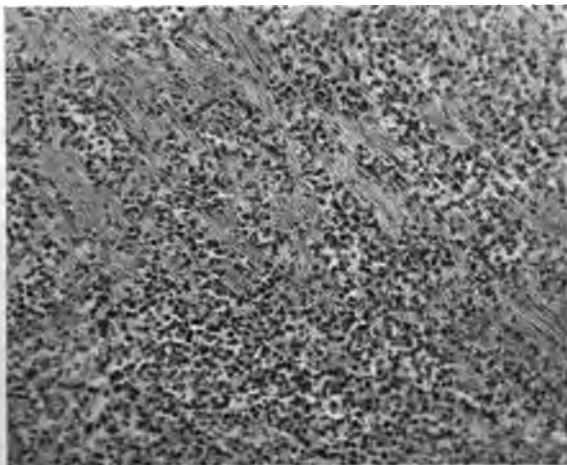


FIG. 193 (Case A23200).—A section through the edge of an apparently actively growing area. Embryonic epithelial cells enmeshed in fibrous connective tissue. $\times 100$.



FIG. 192 (Case A23200).—A section through the gross specimen showing well encapsulated adenoma with degenerating center, marked fibrosis, and some hyalinization, only small areas showing active growth.

NONMALIGNANT ADENOMA

Case 31 (A28462). A woman, aged sixty-five years, had had a gradually growing goiter for thirty years. A cystic adenoma of the left lobe was enucleated. Five hundred twenty-four grams of tissue were removed. The patient has remained perfectly well during the eleven years since operation.

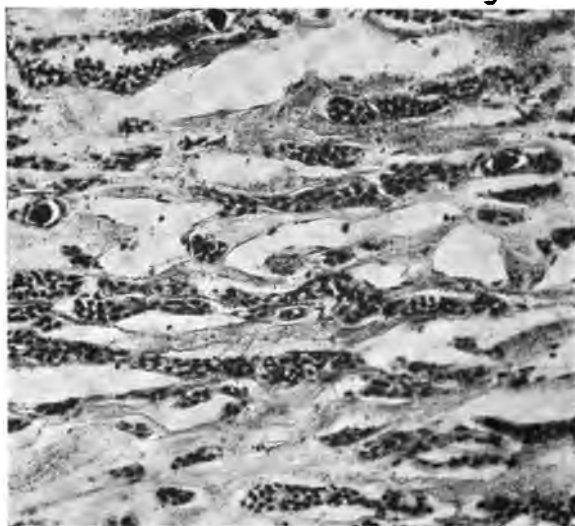


FIG. 194 (Case A28462).—A section through the outer portion of the thick cyst wall showing embryonic cells enclosed in heavy bands of fibrous connective tissue. $\times 100$.

Case 32 (A77623). A woman, aged forty-one years, had had goiter for fifteen years without recent accelerated growth. A cystic adenoma of the right lobe was enucleated. Fifty grams of tissue were removed. The patient reports that she is in perfect health with no local recurrence of tumor up to eight years after the operation.

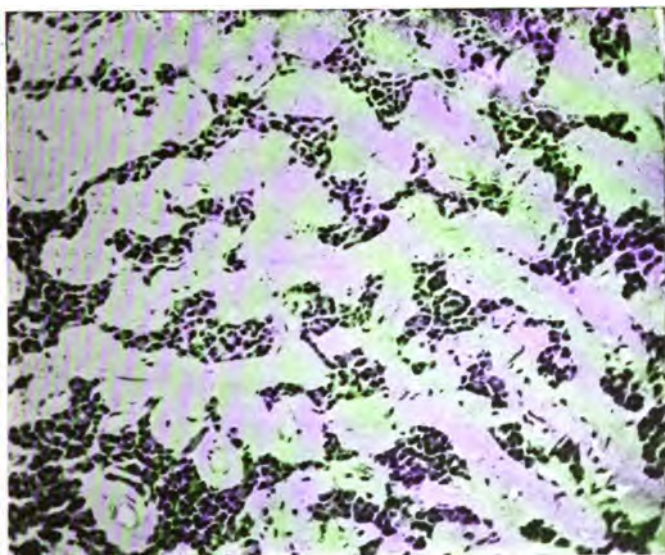


FIG. 195 (Case A77623).—Small embryonic cells in the broad bands of hyaline connective tissue. $\times 100$.

NONMALIGNANT CYSTIC DEGENERATING ADENOMA

Case 33 (A93491). A woman, aged twenty-two years, had had goiter for two and one-half years. A cystic degenerating adenoma of the left lobe of thyroid was enucleated. Sixty grams of tissue were removed. The patient is in good health without local recurrence seven years after operation.

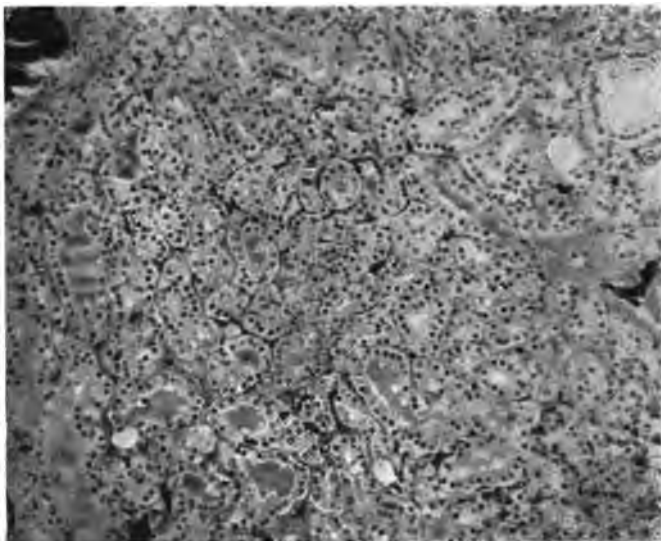


FIG. 196 (Case A93491).—A section through the wall of the cystic thyroid showing degenerating epithelial cells with granular protoplasm and shrunken nuclei arranged in well-defined lobules. $\times 100$.

DEGENERATING CALCAREOUS ADENOMA

Case 34 (A100637). A man, aged forty-nine years, had had goiter for one and one-half years. The right lobe and isthmus were extirpated and a calcareous adenoma involving almost the entire right lobe of the thyroid was enucleated. The right lobe projected a few inches beneath the sternum. One hundred forty grams of tissue were removed from the right, and sixty grams from the left. The patient is alive and well with no local recurrence up to six years after operation.

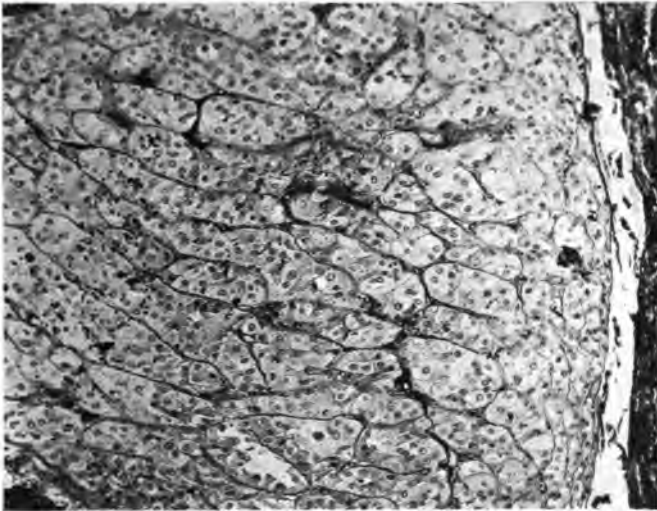


FIG. 197 (Case A100637).—A section through the periphery of the adenoma, including the capsule, near the calcified area, degenerating epithelial cells in well-marked lobules $\times 100$.

DOUBTFUL

Case 35 (A30296). A woman, aged twenty-eight years, had had goiter for twenty-one years. It had not caused trouble until six years before. The growth had been rapid during the past two years. She had lost ten pounds in weight in the past year. The



FIG. 198 (Case A30296).—A section through the right lobe of the thyroid, showing small adenomas included in apparently normal tissue.

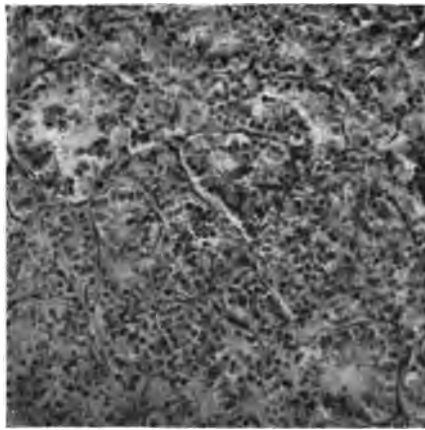


FIG. 199 (Case A30296).—A section through one adenoma shown in Figure 198, showing partially differentiated embryonic epithelium in well-marked lobules, several of which contain colloid. $\times 100$.

right lobe and isthmus were extirpated. One hundred fifty-six grams of tissue were removed. The patient returned for examination eight months after the operation. The goiter had markedly increased in size. The left lobe was resected. One hundred twenty grams of tissue were removed. The patient was examined five months after the second

operation. She was complaining of choking, palpitation and dyspnea, and had lost weight during the last week. Two and one-half years after the second operation she reported that she was the same as when last examined, still had a choking feeling, but

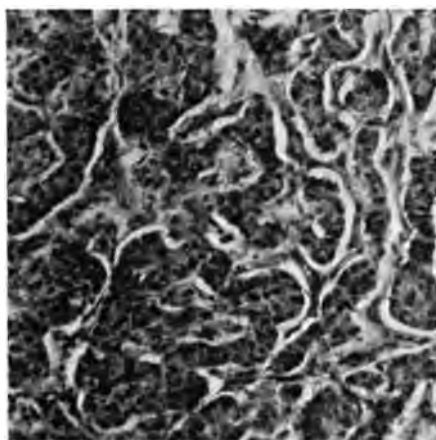


FIG. 200 (Case A30296).—A section through another small adenoma shown in Figure 198, showing partially differentiated embryonic epithelium in lobules between heavy bands of fibrous connective tissue. At first sight this looks like an infiltrated carcinoma. $\times 100$.

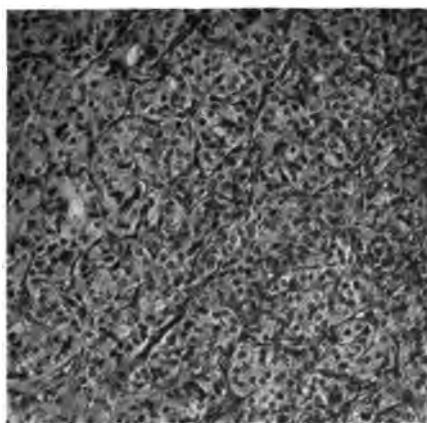


FIG. 201 (Case A30296).—A section through an adenoma removed at the second operation, fairly well differentiated embryonic epithelium arranged in lobules with well-marked vessels between. $\times 100$.

was not losing weight. Seven years after operation she was still having trouble with breathing, but felt better. Ten years after operation she reported no definite symptoms of recurrence; her general health was good.

PROLIFERATING ADENOMAS (WUCHERENDE STRUMA, LANGHANS)

A careful study of a large series of tumors of the thyroid leads inevitably to the conception of the very important part played by proliferating adenomas as the starting point of malignant tumors of finally varying histologic types. This has been shown in the preceding illustrations of specimens from illustrative cases. We are indebted to Langhans for the first detailed description of proliferating adenomas, although they had been observed previously by von Eiselsberg, Erdheim, and many others. Langhans' description is so good that one cannot do better than to repeat it in part. The reader should compare the description with the preceding illustrations, particularly Figures 185 to 193 for embryonic types and Figures 180 to 184 for more differentiated types.

"Microscopically wucherende Struma forms large encapsulated, roundly oval or somewhat flat nodules which may reach a diameter of ten or fifteen centimeters or more. The surface is smooth or has flat projections which are attributable to its lobular structure. The lobules have a diameter of one to two centimeters and are divided from each other directly under the capsule by penetrating fibrous septa; toward the interior they often run together; the septa become perforated. Sometimes they (the septa) are very little developed in the periphery and are suggested only by indentations. In the centers of the nodules there are very often found more or less extensive loosely built connective tissue, somewhat stellate cicatrices. The neoplastic tissue is soft, often hypertrophic, of only medium transparency, and, according to the blood content, gray, red, or pale. The surface of the cut section is smooth or slightly granular.

"The epithelial masses, in fifteen micron sections, show uniform cloudy, finely granular protoplasm with very dense round nuclei. Red outlines between the nuclei are to be seen only in places where they are further separated from each other. In thinner sections the cell outlines can be seen more easily, particularly with oil immersion lenses. The nuclei are round or slightly oval; the smaller ones measure six to eight microns, the larger ones ten and often fifteen microns. The latter usually show a distinct eosin-red nucleolus. The number of chromatin granules and threads is moderate. The nuclei in general are very numerous and are in contact with each other or separated by only a small fraction of their own diameters. There are also, not rarely, small dark nuclei which are usually lying singly between the other nuclei in varying numbers in the younger parts of the tumor as well as in the center in which they are even more frequent. In the region of the central loose 'cicatrix' they are particularly abundant. They also show small clumped, poorly preserved mitoses.

"This nuclei-rich protoplasm is divided by septa, of only blood-vessels with sinus-like lumina, into smaller subdivisions. Between the septa and the epithelium is usually a space, probably the result of retraction of the protoplasm and collapse of the vessel walls. The subdivisions are polyhedral, roundish compartments or long band-like strips.

"The compartments are developed equally in all directions and have a diameter of 200 to 500 microns or even smaller. The majority are very regularly polyhedral with rounded corners. When sections are made radially or parallel to the capsule, the picture is the same. Therefore, they are not cord-like structures, but are closed off from

one another, in this respect being repetitions of normal thyroid vesicles on an enlarged scale.

"The band-like strips vary in their width more markedly than the compartments. Their width is usually less than the diameter of the compartments, 100 microns or less. Rarely have they even five densely arranged nuclei in their transverse diameter. All that are vertical to the capsule of the tumor are parallel to each other and can be easily traced from one to several millimeters; in the depths they are bound by transverse and oblique short branches.

"Compartments and bands may be present in combination. In such cases the bands have a very irregular course, being wound in all directions. The compartments may also be very various; they acquire semicircular sinuosities, become rosetted, or form papillæ-like and finger-like processes, coming out from one or several sides.

"The wide septa through the lobules are essentially fibrous.

"The septa between the epithelial compartments and bands have a very characteristic structure, which is always repeated in the metastasis, and because of that fact one may make a positive diagnosis from a small portion. They are made up of vessels with mere capillary walls. Often there is a loose fibrillary adventitia. Their form is likewise characteristic of these vessels. Only very rarely does one see the transverse section of the vessel or a round group of nuclei which might correspond to the endothelium of a collapsed vessel. Always visible luminæ are cleft-formed and a good many of the polyhedral fields have on each side a single such lumen which gaps more or less widely. It is a markedly flattened sinus-like vessel resembling in some respects the blood-vessels of many sarcomas which also form small spindle-shaped or stellate clefts.

"Normally there may be smaller lacuna-like formations, 'sinusoids.'

"Stages are noted in which all of the previously solid compartments and bands have been changed to numerous small round gland vesicles. Often the vesicles are so dense that one can see the dividing septa only on high magnification. The septa having been changed, they now are nucleolar instead of solid cell masses, a number of pure epithelial hollow spheres, each one of which is surrounded by only one layer of cells which lie more or less loosely near each other and without any vessel-containing septum between them. These pictures are particularly important.

"Colloid is found even in the gland vesicles; first in the form of a uniformly small line stained with eosin which outlines the protoplasm from the luminæ, or in the form of a crescent which fills one-half or two-thirds of the lumen and with its pointed ends surrounds the entire periphery of the latter.

"Therefore, in the final stage of the process a new tissue is built that greatly resembles normal thyroid tissue and still more accurately resembles the tissue of a colloid struma. Therefore, for wucherende Struma the first stage of the large solid cell masses and the final stage of groups of loosely lying gland vesicles without dividing septa are of great importance.

"I have assumed that the earlier stages are on the periphery and the later ones in the center of the nodule.

"In wucherende Struma we have a structure which in its regularity recalls a normal organ that is undergoing development; in the periphery the solid cell mass which disintegrates toward the interior into smaller cords and then into gland vesicles with one-layered epithelium and sometimes with colloid. We have, therefore, a tissue that is constantly being transformed. In addition, we have a vessel with a characteristic form, arrangement, structure of walls, and relationships to epithelium. In its architecture wucherende Struma resembles the normal organ much more than it resembles carcinoma.

"Is it formed, as is assumed to be the case in all malignant struma, on the basis of

colloid nodule which suddenly begins to grow and increases in size and in consistency only as a result of severe stretching of the capsule? . . . I have seen no pictures which proved the origin of neoplastic cells from the epithelial cells of the gland vesicles. The general theory regarding the origin of malignant strumæ from accompanying colloid strumæ finds no basis in my investigations. The facts can be better understood if we assume that the wucherende Struma is such from the very beginning, that even in the earliest stages it consists of solid cell masses and that, therefore, it is to be traced back to that fetal period in which no gland vesicles had been formed and only solid cell masses are present. The process which takes place in wucherende Struma is certainly an incomplete parallel to that of the normal development of the thyroid. You may regard it as a delayed development from fetal rests."

BIZARRE GROWTHS IN DISTANT ORGANS

Previous observers have noted the occasional occurrence of malignant tumors composed of thyroid tissue growing in regions distant from the thyroid with total absence of any appearance of malignant tumor in the thyroid itself. The series of 290 cases herewith presented contains only one case of this kind (Case A300801), a woman, aged thirty, who came to the Clinic with a history of periodic hemoptysis, "vicarious menstruation." Roentgenograms showed a right-sided mediastinal tumor about 7 cm. in diameter, not connected with the circulatory mechanism. A provisional diagnosis of intrathoracic thyroid was made. Operation was refused. Thyroxin was administered and very effectively controlled the hemorrhages for six months, after which time they recurred. The patient returned for examination one and one-half years after she was first seen. The tumor had materially enlarged and the patient was *in extremis*. The mediastinum was explored, but no attempt was made to remove the growth. The patient died one week later. At necropsy a tumor of thyroid tissue of the embryonic adenoma type, 7 cm. in diameter, completely encapsulated, and encroaching on the right bronchus, was found. The thyroid itself was normal except for one small degenerating adenoma, about 1 cm. in diameter, which did not appear to be malignant. Tumor tissue was not found elsewhere in the body. This was apparently an instance of the overgrowth of fetal tissue which had probably been misplaced into the lung in the embryo.

Not rarely the epithelial cells in the thyroid tissue of metastasis are not in the same stage of development as that in the original tumor in the thyroid. A good illustration of this is found in Case A355859, of the series of 290 cases, a man, aged sixty-two, who came to the Clinic *in extremis* and died two days afterward. Necropsy showed the

lungs, pleura, liver, and abdominal lymph nodes filled with extensive metastatic deposits of tumor tissue, the cells of which in their size, staining, and arrangement resembled those in proliferating fetal thyroid. The thyroid itself was the site of an extensive malignant tumor, most of the tissue of which was composed of cells fairly well differentiated toward the adult type.

RECURRING THYROID TUMORS OF DOUBTFUL MALIGNANCY

The series of 290 cases contains three or four instances of young persons with rapidly proliferating tumors of the thyroid which histologically are either fetal or partially differentiated adenomas which recur rapidly and extensively and yet throughout long periods show no signs of metastasizing (Case 35 (A30296) Figs. 198 to 201). One should be warned in diagnosing the condition shown in Figure 200, an infiltrating adenocarcinoma. The histology of the tumors in the other cases usually resembled that shown in Figures 199 and 201, but though recurrences have been frequent throughout periods of from eight to fourteen years, there is still no evidence of metastasis.

HYALINIZATION, FIBROSIS, CALCIFICATION, AND HYDROPIC DEGENERATION

There can be no question but that many proliferating embryonic adenomas, which apparently start on their way toward malignancy, become impeded in their active overgrowth, reduced and finally degenerate, either by hyalinization, fibrosis, calcification, or hydropic change. Good illustrations of this are seen in Cases 30 to 34 (Figs. 192 to 197), in which the relative amounts of connective tissue and parenchyma should be noted, as well as the cells with small, cramped, irregular nuclei without mitosis. The pathologist must take this possibility into account in his advice to the surgeon, but a proliferating adenoma in a patient of cancer age should not be considered benign unless the process of degeneration is very extensive and thoroughly overbalances the proliferation. The gross appearance of the tumor, the thickness and integrity of the capsule, the relationships of the capsule and fibrous septa to the parenchyma, the presence or absence of hyalinization, fibrosis, calcification and anemic or hydropic degeneration, the character and arrangement of the parenchymal cells, and the presence or absence of mitotic figures must all be taken into account.

SUMMARY

1. The paper presents an analysis of the literature and a summary of the data on 290 patients with malignant tumors of the thyroid who have been examined in the Mayo Clinic up to December 31, 1920.

2. Malignant tumors of the thyroid are much more frequent than is generally believed. Their correct clinical diagnosis is often missed (a) because they may have periods of development of from five to fifteen years and patients are not followed up long enough after operation, and (b) because not infrequently the tumor in the thyroid itself is relatively small and the character of metastasis is not determined, owing to the rarity of necroses.

3. Pathologic diagnosis is difficult owing to the great variation in the histology of the tumor tissue and its resemblance to that of non-malignant processes.

4. There has been a marked failure of American surgeons to report in the literature their cases of malignant tumors of the thyroid; this should be corrected.

5. Insufficient observations are at hand for determining the geographic incidence.

6. The age incidence at the date of diagnosis is greatest in the fifth decade.

7. The distribution by sex is about one man to two women.

8. Patients usually seek medical advice on the occasion of recent rapid growth in a long-standing nodular tumor of the thyroid. Some give histories of slow continuous growth.

9. Early thorough operations give a fair percentage of cures. Palliative operations in late cases with extensive local involvement are warranted.

10. Pathologic diagnosis must take into account the usual development of malignant tumors of the thyroid from proliferating embryonic adenomas.

11. A series of photographs of specimens, gross and microscopic, of thirty-five illustrative cases is presented with brief clinical and pathologic notes to serve as an atlas in assisting the pathologist in diagnosis.

12. The pathologist must be thoroughly familiar with the characteristics of proliferating adenomas, as first described by Langhans, in all their stages.

13. The pathologist must be on the lookout for the possible relationship of bizarre metastatic growths of tumors of the thyroid.

14. The pathologist, in his diagnosis for the guidance of the surgeon, must consider the relative preponderance of proliferative and degenerative processes in the tumor, but a proliferating adenoma in a patient of cancer age should not be considered benign unless the process of degeneration is very extensive and thoroughly overbalances that of proliferation.

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BLOOD

THE BLOOD CHOLESTEROL, ITS IMPORTANCE, AND THE VALUE OF ITS DETERMINATION IN CANCER RESEARCH*

GEORGINE LUDEN

The cancer problem is undoubtedly one of the greatest problems of civilization, and its solution of the utmost importance because of the innumerable victims of malignant growth. The value of studying the functional efficiency of the body structures, rather than their morphologic appearance, has been recognized in many fields of modern medicine. It is no longer a matter of debate that, in diabetes, for instance, histologic examination gave but little information, even when the pancreas itself was studied, whereas the chemical analysis of the blood and the urine not only revealed the nature of the disease, but insured far more successful treatment.

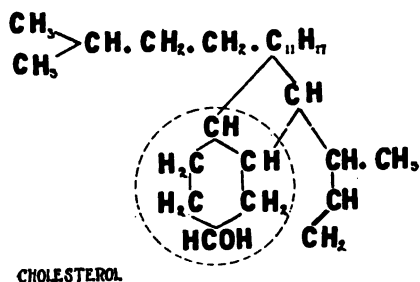
The life of every cell in the body depends upon its blood supply; this is universally conceded. The blood is practically the only food supply to which the cells have access. If it be true that the cells perish and disintegrate when their food supply is cut off, the quality of the food, that is, the chemical composition of the blood, must of necessity affect the welfare of the cells. It cannot but influence them "for weel or woe." The researches of many investigators have proved that the blood contains numerous chemical constituents: proteins and their derivatives, glucose, inorganic salts, and lipoids, such as lecithin and cholesterol. It is obvious that the relative proportions in which these chemical constituents are present in the blood will play an important part not only with regard to the general welfare of the body as a whole but also with regard to the growth, the differentiation, and the rate of proliferation of the individual cell units.

The blood cholesterol, one of the chief blood lipoids, deserves special consideration because it is intimately associated with the prob-

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lems of growth and cell proliferation and of resistance to bacterial invasion. Cholesterol is a well-defined chemical entity. The cholesterol molecule ($C_{27}H_{46}OH$) is a complex structure (Robertson and Burnett²³) (Fig. 204).

Cholesterol appears to be a substance which the body cannot afford to be deprived of, for Dezan's experiments showed that mice fed on an entirely cholesterol free diet succumbed after apparently synthesizing cholesterol for a short time; cholesterol was found in the feces during the cholesterol free diet, the mice increased in size and weight, and their total cholesterol content augmented by one-third, but they all died at the end of seventeen days. Since all animal cells contain some cholesterol, and practically all the staple foods as well, though in varying amounts, a total cholesterol deficit is not likely to occur in the human body. Reserve deposits of cholesterol occur, moreover, in



CHOLESTEROL

FIG. 204.—Graphic formula of cholesterol according to Windaus and von Fürth, cited by Robertson and Burnett.

the body fat, the brain, the suprarenal cortex, and the liver, so that the synthesis of cholesterol must be looked upon as an emergency measure, under strictly experimental conditions, which it would be difficult to duplicate in every-day life.

Cholesterol and cell proliferation.—It has been shown by the work of Dorée, Ellis, Gardner, Fraser and Lander,^{11, 12, 13, 14, 15, 16, 17} of Browder, and of Robertson and Burnett²⁷ that cholesterol takes an active part in cell proliferation. Whether it acts as a catalyzer, as Robertson and Burnett have suggested, or whether it is merely used up as building material in the formation of cells, is not known definitely. The experiments of Ellis and Gardner, who incubated hen's eggs for different periods and showed by determinations that the cholesterol content of the egg yolk diminished parallel with the increase of the volume of the chick embryo, make it seem probable that cholesterol is used directly

for the manufacture of cells. Browder added cholesterol to the culture medium of paramecium and found that the rate of division of these one-cell organisms was increased from one and one-third to five times, as compared with controls grown in the same culture medium, but without the addition of cholesterol. Robertson and Burnett²⁷ in experimenting with tumor-grafted rats, showed that intravenous injections of cholesterol in sodium oleate cause the tumors in the injected animals to grow twice as fast as in the controls, all the rats having been

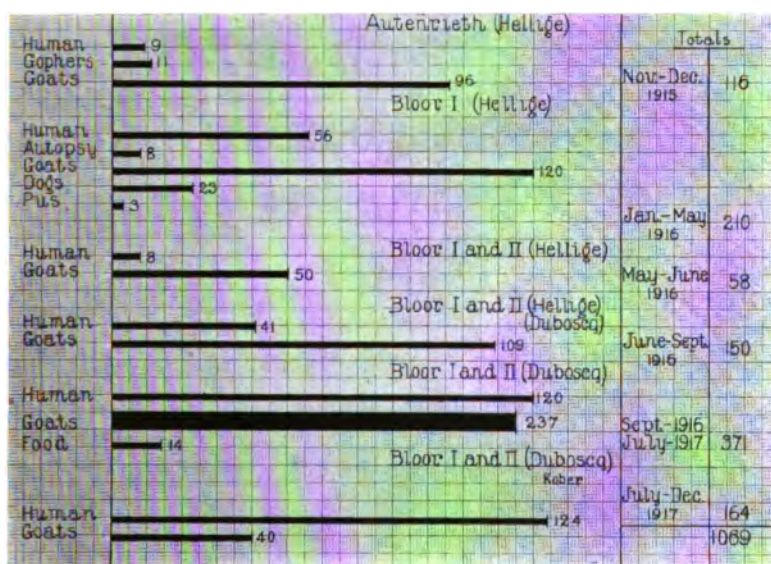


FIG. 205.—Cholesterol determinations made by the writer from 1915 to 1917 by Autenrieth-Funk and Bloor I and Bloor II methods. Hellige, Hellige-Duboscq, and Duboscq-Kober colorimeters were used. The colorimeters used are noted in parentheses. The fourth entry from the bottom is drawn in double width on account of the number of determinations made: goat's blood 237.

grafted at the same time and with the same tumor. Aschoff, Autenrieth and Funk, and, very recently, Chauffard, Laroche, and Grigaut, called attention to the increase of the blood cholesterol during pregnancy and to its return to normal after delivery; Bacmeister and Havers demonstrated a similar increase in the blood of pregnant bitches, with return to normal after the pups were littered.

Investigations of the writer.—The fact that in Robertson and Burnett's²⁷ experiments on rats the injected cholesterol was manifestly carried to the tumor cells by the blood, because the injections were made

intravenously on the side of the animals as far removed from the graft as possible, led me to investigate the cholesterol content of the blood in malignant conditions, and to study the factors which might influence the blood cholesterol. The problems involved proved far more numerous and more complex than I had anticipated.^{19, 20, 21, 22, 23, 24} Between 1915 and 1921 more than 3,000 samples were analyzed for cholesterol. The samples comprised the blood of human beings in health and in disease and under experimental conditions; the blood of goats, gophers,

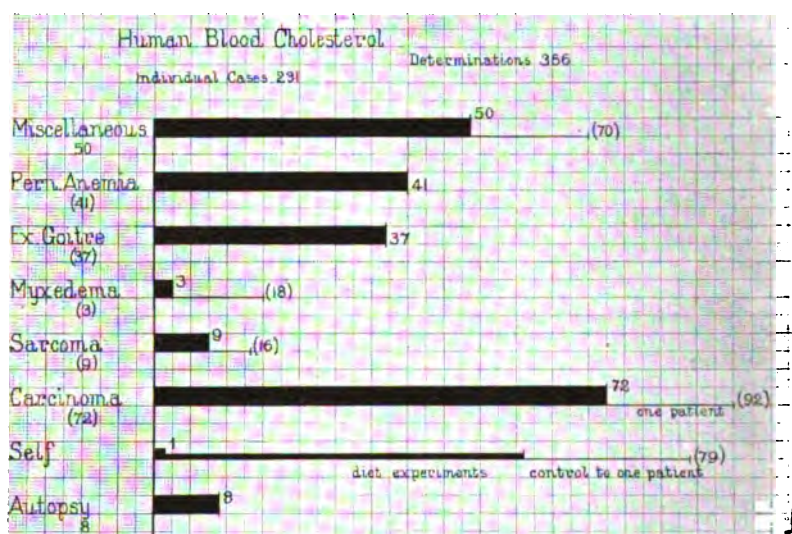


FIG. 206.—Determinations of cholesterol in the human blood under various conditions. The wide bar denotes the number of individual cases; the narrow bar and number in brackets denote additional determinations on the same patient. Autopsy: The blood was taken in eight cases at different hours after death in order to study the effect of post-mortem changes; the cholesterol values were unchanged.

dogs, and rabbits; blood taken at necropsy, several hours after death, and pus, bile, and food-stuffs. Since two determinations at least were made on every sample the series represents between 6,000 and 7,000 determinations (Figs. 205, 206, and 207).

Cholesterol and bacterial infection.—If the cholesterol content of the blood promotes the multiplication of cells by some as yet unexplained mechanism, it may be said to have the opposite effect on the growth of pathogenic bacteria. Manfredi showed that the addition of cholesterol to the culture medium (agar-agar) completely inhibited the growth

of many pathogenic bacteria if a concentration exceeding 50 : 10,000 was used. Concentrations of 20 : 10,000 had an inhibitory effect in the majority of cases, although *Bacillus prodigiosus*, *Bacillus typhosus*, and *Staphylococcus aureus* managed to thrive even in these concentrations. Concentrations exceeding 10 : 10,000 greatly reduced the growth of many types of bacilli and streptococci (*Bacillus puerperalis*, *Bacillus diphtheria*, *Streptococcus erysipclatis*) and of the cholera spirillum. Manfredi's observations have recently been corroborated by the clinical investigations of Sisto, who found a constant cholesteremia in

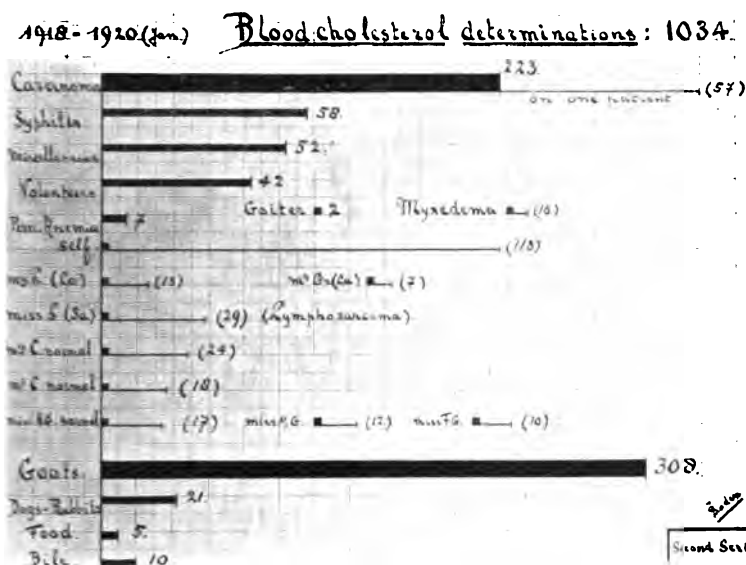


FIG. 207.—Cholesterol determinations made by the writer from 1918 to 1920. Wide bar denotes number of persons. The narrow bar and number in brackets denote additional determinations on the same person.

typhoid fever, which only receded during convalescence, a marked increase of the blood cholesterol in pneumonia at the onset of the disease, but inconstant findings in pulmonary tuberculosis, exacerbations being accompanied by a rise in the blood cholesterol values. I was able to observe an increase of the blood cholesterol at the onset of symptoms in several patients during the epidemics of influenza in Rochester in 1918, 1919, and 1920. Low blood cholesterol values prevail, on the contrary, in chronic bacterial infections such as tuberculosis, when there is no temporary exacerbation, and in syphilis. It

is interesting in this connection that erysipelas has been known to exert a curative influence in malignant conditions, and that Coley's treatment, by which a cure has been wrought in 10 per cent of the cases treated, consists of injections of *Bacillus prodigiosus* and *Bacillus erysipelatis*. The blood cholesterol, therefore, seems comparable to the financial resources which, if properly used as the wealth of a nation should be, insure the welfare of the community, and which if badly handled become a curse, but which in emergency may be utilized to ward off foreign invasion. The increase of tumor formation and the great number of recurrences following the epidemics of influenza may have to be interpreted as evidence that the organs regulating cholesterol metabolism have been overworked in the fight against the infection with resulting mismanagement of cholesterol metabolism.

The value of blood cholesterol determinations.—The test for cholesterol in the blood is not a diagnostic test. This must be borne in mind. It is comparable in this respect with many valuable clinical tests, for example, the Wassermann test, and the test for albumin in the urine. Neither the Wassermann test nor the test for albumin furnishes a clear-cut diagnosis in the absence of corroborative clinical evidence, for we know that a positive Wassermann reaction may occur in certain cases in which all possibility of syphilitic infection has been excluded, in tuberculosis, and in pernicious anemia. Albumin in the urine does not furnish a differential diagnosis in cases of cystitis and nephritis without further information based on other clinical data. Yet the value of the Wassermann test and of the test for albumin is beyond dispute. Thus, in blood cholesterol determinations, the detection of high cholesterol values accompanied by "gallstone symptoms" does not give conclusive evidence concerning the presence or the absence of stones, although gallstones contain from 80 to 95 per cent cholesterol and are crystallization products of the cholesterol in the bile. Since the liver carries about one-third of the total blood volume and the bile is furnished by the liver, the cholesterol content of the blood must influence the cholesterol content of the bile. But, as Rothschild and Rosenthal have pointed out, in cases of cholelithiasis three possibilities should be taken into account in the interpretation of the blood cholesterol values: (1) high blood cholesterol values, no stones being found at operation because the gallstones have not had time to form; (2) low blood cholesterol values accompanied by the finding of stones at operation, which indicates that the cholesterol content of the blood

has been reduced because the cholesterol was used for the formation of stones; and (3) high blood cholesterol values and stones in the gall-bladder, showing that an opportunity exists for the formation of more stones, especially if the high cholesterol values remain constant even

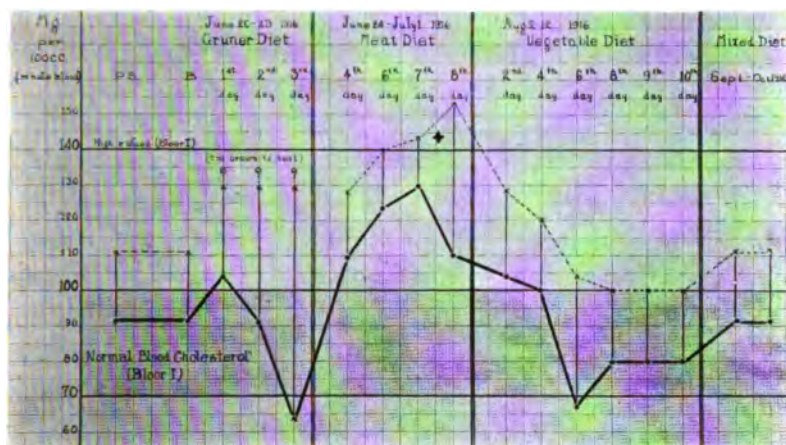


FIG. 208.—Cholesterol determinations on the writer. P. S. Personal cholesterol standard from January to June, 1916. The tests were made at irregular intervals and showed practically no variations. B. Test made on the day preceding the experimental diets.

Gruner's diet: Milk and water, bread, lettuce. The Bloor II values (?) could not be determined, the color reaction being brownish green because of the great amount of "changed" cholesterol. The Bloor I values dropped rapidly. The Bloor I values are indicated by the solid line, the Bloor II values by the dotted line.

Meat diet: Meat was used exclusively for every meal; only a very small piece of bread had to be taken "to help the meat down" toward the end of the experiment, when meat became very repugnant. Attacks of diarrhea, lowering Bloor I, but increasing Bloor II cholesterol values.

Vegetable diet: Vegetables and fruit exclusively. Observe the drop of the Bloor I values and satisfactory amount of "changed" cholesterol (vertical line). No diarrhea intervened during the vegetable diet, but the blood cholesterol settled down to a lower level.

Mixed diet: Meat twice a day, vegetables and fruit; usual type of mixed diet. The blood cholesterol returned to its former level. During all the dietary experiments coffee and tea were taken in the usual amounts, but, as usual, no alcohol.

after cholecystectomy. It is in the latter instance that determinations of the blood cholesterol are of special importance, because the persistence of high values shows that the patient is suffering from a more or less permanent impairment of cholesterol metabolism and because the cholesterol content of the blood can be reduced by dietary measures,

as Rothschild and Rosenthal have shown, and as I was able to corroborate by a series of dietary experiments on myself²² (Fig. 208). It is not surprising that eggs should further cholesteremia: the cholesterol concentration of the egg yolk is roughly ten times that of normal human blood, 900 mg. per 100 c.c. It is not easy to understand, however, why meat should increase the blood cholesterol to a marked extent, as the cholesterol content of meat is very much lower than that of eggs, and the cholesteremia produced by a diet consisting of Scotch oatmeal exclusively would be wholly inexplicable but for the work of Howard Mueller, because oatmeal contains no cholesterol whatever. Mueller showed that both in vivo and in vitro the chemical character of cholesterol is changed by the influence of the bile and of the pancreatic juice. Bile transforms about one-third of a given amount of cholesterol into cholesterol esters; pancreatic juice converts two-thirds of the cholesterol into esters, but the combination of bile and pancreatic juice causes the esterification of the total amount of cholesterol. This was found to apply in test-tube experiments as well as in experiments on animals by ligation of the bile ducts or the pancreatic ducts respectively. It seems possible that an excess of carbohydrates, by overworking the pancreas, may prevent the proper esterification of the blood cholesterol and its subsequent elimination, with a resulting increase of the cholesterol concentration in the blood, such as I observed during my oatmeal diet. All the problems involved in the relation between the diet and the blood cholesterol cannot be discussed here; these problems are numerous and intimately connected with the relative efficiency of the pancreas, the liver, the adrenals, and other glands which are concerned in cholesterol metabolism. From a practical point of view it would seem a safe proceeding, however, to advise patients suffering from cholestermia to reduce the intake of eggs, meat, oatmeal, and of cholesterol-rich fish, black bass and salmon, and to use, temporarily at least, a diet composed chiefly of fruit, vegetables, and milk, blood tests being made to check the effect of the diet.

Experiments on animals showing stimulation of tumor growth by cholesterol.—The dietary experiments of Corson-White on a large series of rats, all grafted with the same strain of a Flexner-Jobling adenocarcinoma, furnish conclusive evidence of the stimulation of tumor growth by cholesterol. Corson-White found that "diets which stimulate most markedly the growth of large tumors (after transplantation)

give normal growth curves in normal rats, show a diminution of the number of lymphocytes in the circulating blood and a cholesterol content equal to or higher than normal," and that "those diets on which rats produced the most metastasis gave the highest (blood) cholesterol values." He determined the cholesterol content of the total blood volume by the Bloor method after killing the animal, as it is impossible to obtain a sufficiently large sample of blood from the veins of a rat,

Average Size of Tumors in mm. at end of 30 days.		Metastases.	Takes.
		%	%
██████████	Normal Diet + Vitamines.	0	87.2
██████████	" " (castrates).	0	87.4
██████████	" " + Cod-liver oil.	82	91.7
██████████	" " + <u>cholesterol</u> .	94	91.9
██████████	" " + olive oil.	78	91.2
██████████	Oats Diet.	0	72.4
██████████	Normal Diet.	0	87.2
██████████	Intervient Diseases.	0	61.4
██████████	Mendel - Osborne Diet + <u>cholesterol</u> .	0.4	26.6
██████████	Mendel - Osborne Diet.	0	77. -
██████████	Normal Diet + Sudan III	0	14.7
██████████	Underfed - normal Diet.	0	28. -
██████████	Egg and Milk (inadequate diet)	0	12. -

Corson-White 1919 - Pennsylvania Med. J. XXII - 312-332 : Diet and Cancer.

FIG. 209.—Corson-White's dietary experiments on rats grafted with the same strain of a Flexner-Jobling adenocarcinoma. Growth-stimulating diets above the central dividing line; inadequate, growth-retarding diets below the central dividing line. The number of takes and cases of metastasis is markedly increased by addition of cholesterol to the diet and by the addition of cod-liver oil and olive oil. According to Chauffard's observations fats are transformed into cholesterol.

3 c.c. being needed for Bloor's cholesterol determination. The experiments of Corson-White comprised two types of diets: a normal, adequate diet giving normal growth curves in the controls, and the inadequate diet (Mendel-Osborne) on which the animals remained in good condition, but did not grow. Addition of cod-liver oil, olive oil, and cholesterol to the normal, adequate diet produced a higher percentage of "takes" and more extensive metastasis (91 per cent) than the normal diet alone (87 per cent); but the addition of the cholesterol furnished

the highest percentage of metastasis (94 per cent) in conjunction with the normal diet, and even produced metastasis (0.4 per cent) in combination with inadequate diets, which otherwise gave a small number of takes and seemed to inhibit the development of metastasis (Fig. 209). These findings fully corroborate the observations of Robertson and Burnett (which formed the basis of Corson-White's work), of Rothchild, and my observations in experimental diets and on the blood of patients suffering from cancer. The stimulation of tumor growth by ingestion of olive oil and cod-liver oil is explained by the investigations of Chauffard, Laroche and Grigaut,⁵ who found a marked increase of the blood cholesterol after the ingestion of fat, even when the fat contained no cholesterol. This suggests that there is an intra-organic synthesis of cholesterol from fat. The observations of Corson-White, that "in rats on oats (inadequate diet) the actual tumor mass was heavier than the entire gain in weight of the animal during the diet period," not only explains the results of Stahr, who produced large carcinomas of the tongue in rats by feeding oats exclusively, but also the marked rise of my blood cholesterol during my oatmeal diet experiment,²² and suggests the advisability of excluding oatmeal (porridge) from the diet of cancer patients.

Factors that influence the blood cholesterol.—Cholesterol metabolism is regulated by the activity of several organs, namely, the liver and the pancreas; but the suprarenals, the gonads, and the thyroid may play an even more important part. The suprarenals are probably the chief regulators of cholesterol. The gonads might be termed the principal market for cholesterol, and it is not surprising that disturbances of cholesterol metabolism should be particularly likely to occur when the gonads are either heavily taxed by work, as in pregnancy, or when their activity is declining, as in the menopause. I need but mention the well-known "pregnancy gallstones" and the frequency of malignant growth when reproductive activity ceases. The thyroid has been called the "dynamo" and "the pacemaker" of the body (Crile), because of its influence on the basal metabolic rate. It would almost seem a foregone conclusion that the basal metabolic rate, the rate of burning in the body, should influence cholesterol metabolism, but blood cholesterol determinations were needed to show that this obvious conclusion is really correct (Fig. 210). In myxedema the basal metabolic rate and the blood cholesterol values are inversely proportional; in exophthalmic goiter, when the body engine, so to speak, is going at

ninety miles an hour the blood cholesterol values are within the normal and low normal ranges.

Cholesterol determinations should always be made during the post-digestive period, that is, before breakfast, in order to eliminate the temporary increase which is comparable to the digestive leukocytosis. In our determination two tests are made routinely for every blood sample. In the first test (Bloor I method) only the pure or unchanged cholesterol is determined. The second test gives the value of both changed and unchanged cholesterol combined. The difference between

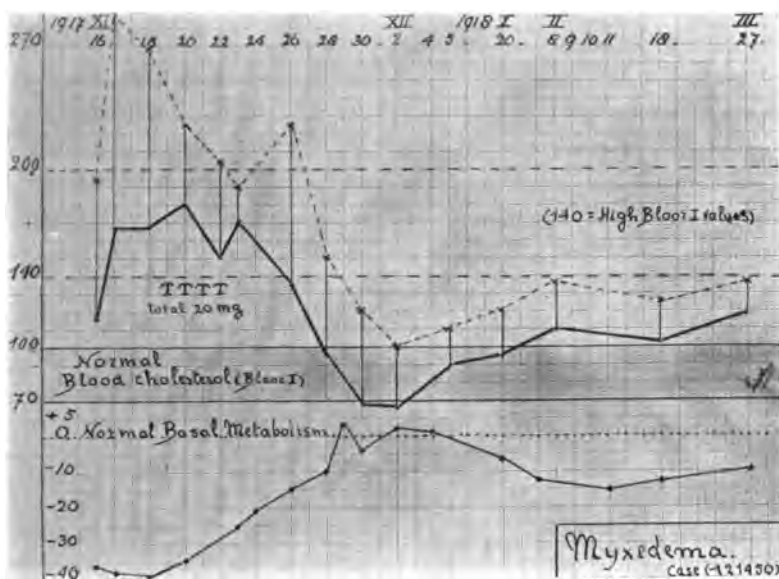


FIG. 210.—The inverse proportion between the basal metabolic rate and the blood cholesterol. The patient, who had a pronounced case of myxedema, became perfectly well after the administration of the thyroid hormone (T), Kendall's thyroxin, 5 mg. at each dose.

the values found in the first test and in the second test (Bloor II method) represents the amount of changed cholesterol or cholesterol split-products contained in the blood. It has been the use of this twofold test which revealed anomalies of cholesterol metabolism in malignancy and furnished evidence that the beneficial effect of radium treatment is intimately connected with changes in the chemical composition of the blood (Luden^{23, 24}).

The anomalies of the blood cholesterol in cancer: the effect of radium.—A twofold disturbance of cholesterol metabolism is found in malignant

conditions, and especially in carcinoma: namely, a tendency to cholesteremia and a lack of cholesterol split-products in the blood. In other words, the body is not handling or burning its cholesterol as it should. The pure cholesterol may be fitly compared to fuel: unburnt fuel is eminently capable of starting a conflagration. The cholesterol split-products are comparable to consumed fuel, or ashes in a general sense; ashes are not suited to keep a fire burning. A comparative study of the blood cholesterol of seventy patients suffering from diverse types of cancer and of seventy patients suffering from nonmalignant conditions showed that high cholesterol values predominate in carcinoma, being accompanied by a lack of cholesterol split-products in the blood, whereas in the nonmalignant cases there was no lack of changed cholesterol and the high values were in the minority. After radium treatment the high values changed to medium, or "inflammatory values," and the amount of split cholesterol in the blood was markedly increased; the lack of split-products disappeared altogether. The effect of radium on the blood cholesterol was strikingly shown by observations in a case of lupus erythematosus, degenerating into carcinoma. Clinically, the lesions on the patient's nose were typical of lupus erythematosus, but treatment with blue light failed to have the usual curative effect. The cholesterol tests revealed a total lack of split cholesterol, suggesting the presence of carcinomatous degeneration. Excision of a minute portion of the lesion and microscopic examination of serial sections confirmed this suspicion (Figs. 211 and 212). Exposure to radium caused the lesions to disappear; cholesterol tests before and after exposure showed that improvement went hand in hand with the activation of cholesterol metabolism (Fig. 213). Two explanations are admissible with regard to the effect of radium on the blood cholesterol. Either the disintegration of the blood cholesterol is caused by the photo-active properties of the radium rays or by the stimulation of the organs that regulate cholesterol metabolism. The experiments of Schulze and Winterstein show that the photographic rays in ordinary daylight produce chemical changes in cholesterol in the test tube; but stimulation of the organs that regulate cholesterol metabolism, resulting in an increased activity of these organs, is strongly suggested by the chemical changes in the composition of the blood, perhaps by the so-called radium sickness, and certainly by the disappearance of metastatic tumors which were not exposed directly to the rays, but located at a considerable distance,

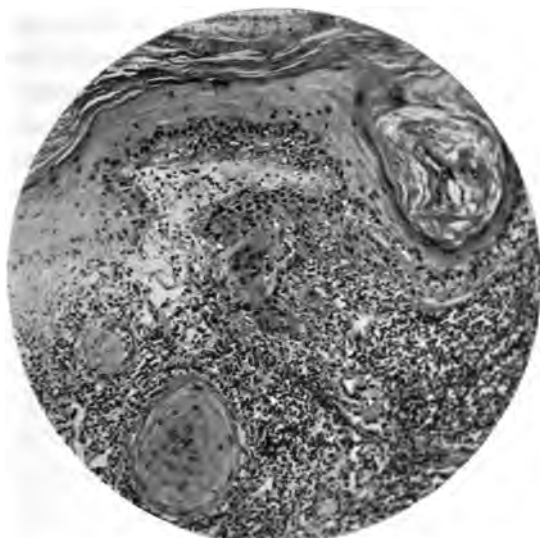


Fig. 211.



Fig. 212.

FIGS. 211 and 212 (Case A192075).—Lupus erythematosus of the nose degenerating into carcinoma; serial sections from biopsy for diagnostic purposes.

the main tumor alone being treated with radium. I have been able to observe repeatedly that patients whose blood cholesterol values did not

show changes "in the right direction" did not appear to derive as much benefit from radium treatments as patients in whose blood a marked increase of cholesterol split-products could be demonstrated. This suggests that dietary measures calculated to reduce the work of cholesterol metabolism in conjunction with radium treatment might enhance the effect of the radium treatment itself, the response of the patient being observed by blood cholesterol determinations.

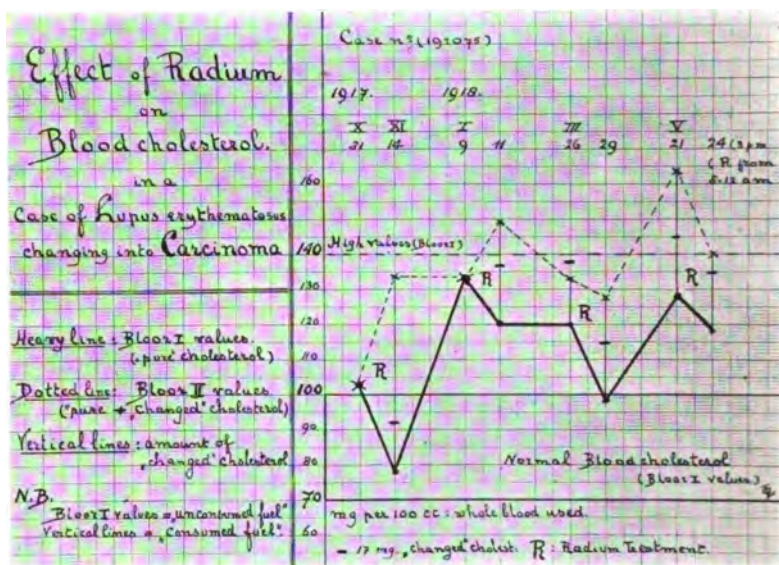


FIG. 213.—The effect of radium treatment on the blood cholesterol in Case A192075. The Bloor I values (heavy line) dropped and the changed cholesterol (vertical line) increased after each radium treatment (R). The small horizontal bar on the vertical denotes the normal minimum of changed cholesterol, 17 mg. per 100 c.c. of whole blood. At the patient's last visit to the Clinic, May 21, the lesion on the nose was barely perceptible, a large amount of changed cholesterol being present in the blood. One more radium treatment was given to complete treatment; the cholesterol determination (May 24) was made three hours after exposure to radium.

Before closing I would like to call your attention to an established fact which I think has received too little consideration, namely, the spontaneous regression of malignancy observed in man. Rohdenburg has published a detailed account of 302 cases in which this phenomenon occurred; in roughly one-third of these cases a microscopic diagnosis was made and the subsequent history "carefully controlled." In every instance the condition of the patient had proved to be inoperable,

"hopeless." No radium treatment had been given and such operations as had been performed are described as "palliative" or "incomplete." Yet tumors and metastasis disappeared and the patients became "clinically well." The importance of this fact can hardly be overestimated. It is proof positive that the human body can wage a winning fight against malignancy under the most untoward conditions. Since outside aid had proved useless, the victory must have been won by inside means. Changes in the body chemistry, resulting from increased or renewed activity of organs by which the chemical condition in the body is regulated, seem to be the only available explanation since the chemical composition of the blood must influence the body cells. If this be true, the cancer problem must be looked upon as a chemical problem and physiologic chemistry may be expected to furnish its ultimate solution. Much work remains to be done, but cholesterol determinations give some information, at least, concerning the efficiency of cholesterol metabolism in a given case; they help to ascertain the effect of dietary measures and the response of the patient's organism to radium therapy; and they may be expected to reveal the organ initially responsible for the disturbances of cholesterol metabolism which are connected with the lawless proliferation of cells found in malignant disease; hence the value of blood cholesterol determinations and their place in cancer research.

SUMMARY

1. Cholesterol is an important chemical constituent of the blood.
2. There is evidence that the blood cholesterol plays an important part by promoting cell proliferation and by combating bacterial invasion.
3. The test for cholesterol in the blood is not a diagnostic test, but it furnishes valuable information concerning the efficiency of cholesterol metabolism.
4. The activation of cholesterol metabolism after radium treatment demonstrated by the blood cholesterol determinations, and the parallel improvement of patients suffering from malignancy indicate that there is an intimate connection between disturbances of cholesterol metabolism and malignant disease.
5. Cholesterol metabolism can also be improved by dietary measures, suggesting that beneficial effects may be expected from dietary meas-

ures tending to reduce the cholesterol intake with the food, combined with radium therapy.

6. Since the life of the cells depends upon their blood supply, the chemical composition of the blood must be equally important; radium treatment changes the chemical composition of the blood, as is shown by blood cholesterol determinations.

7. Spontaneous cures have been observed in well-authenticated, inoperable, "hopeless" cases of cancer; this proves that the body can wage a winning fight against malignant disease; as therapeutic measures had proved ineffective in these cases, some internal readjustment must account for the cures. Chemical investigations will solve the cancer problem by revealing the nature of this internal readjustment.

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BALANTIDIUM COLI AND PERNICIOUS ANEMIA: REPORT OF FOUR CASES*

ARCHIBALD H. LOGAN

Balantidium coli is a flagellate parasite inhabiting the colon, common in animals, especially the pig, but rare in man. The work of Strong, Bowman, Bel and Couret, and Manlove shows that the parasite is capable of invading all layers of the intestinal wall. It has been found in the blood vessels of the intestine and in other organs. With the accompanying bacteria superficial and deep ulcers are formed which cannot be distinguished from ulcers due to ameba until the microscope differentiates the parasite. The parasite also possesses the power of encysting.

The clinical symptoms of invasion by *Balantidium coli* bear a great similarity to those produced by ameba. Both present an acute and chronic form. In the acute form there is severe bloody dysentery, with great loss of fluid and marked toxic action. Perforation may occur. Death follows usually in from a few days to one or two weeks. The chronic form often exists for years with alternating constipation and diarrhea. As with many other parasites the acute form seems to develop chiefly in warm countries and the chronic form in colder regions.¹⁰ The symptoms and findings of pernicious anemia seem to accompany the chronic form of the infection.

The prognosis in the acute form is very bad even if the case is seen early. In the chronic form it seems to be bad only when the syndrome of pernicious anemia is added. Our patients have died from the pernicious anemia rather than directly from the dysentery.

Schwartz finds a hemolytic agent in *Ascaris lumbricoides* and *Trichuris trichiura*, which he believes accounts for the anemia in these infections. Under certain conditions, supposedly including a decomposition of the segments of the worm, *Dibothriocephalus latus* produces a picture of pernicious anemia. If the worm is expelled the blood picture returns to normal.

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Glaessner has found a hemolytic agent in *Balantidium coli*. It seems probable that the constant subjection of the blood-forming organs to the poison is the cause of the pernicious anemia syndrome in the chronic type of case. The removal of the *Balantidium coli* and its hemolytic agent is a far different problem than the removal of the *Dibothriocephalus latus*. Since *Balantidium coli* penetrates the intestinal wall and its blood vessels and other organs in the body and also encysts, we cannot be sure when the organism is eradicated from the stools that it is not harbored somewhere in the tissues of the body with its hemolytic agent still active. Thus if the pernicious anemia complex persists after treatment we cannot be sure whether the toxin of *Balantidium coli* is still active, or whether once the complex is started it becomes an entity.

The treatment resolves itself into ridding the intestinal lumen and the body tissues of the organism. The literature indicates that most of the drugs used against intestinal parasites are without effect on *Balantidium coli*. In our experience in the Clinic with the flagellate *Lambia intestinalis* we found that the only drug that gave any satisfaction was put into the blood in sufficient quantity to act as a direct poison when ingested by the parasite; in a large number of cases arsphenamin proved of great value. In our latest case of infection with *Balantidium coli* we employed arsphenamin with apparently very good effect. An enema with vinegar and tannic acid also was given every day or every second day with the idea of producing an acid medium in the colon and of giving a direct parasiticide. On account of encystment the treatment must be carried out a long time; just how long I do not know, since the length of time the organism may remain encysted and become active again has not been determined. That the living organism is very resistant is shown by Klein, who found actively motile *Paramecium coli* in sewage which had been bottled for three weeks. The patient who was treated by five intravenous injections of arsphenamin at weekly intervals had nine stool tests negative for the parasite, the diarrhea was entirely checked, and he felt very much better; yet the neurologic symptoms of pernicious anemia still persisted. Jennings reports one case with the pernicious anemia syndrome in which the patient was apparently cured after two relapses.

It is interesting in connection with the family histories of three of our patients that death of one or more parents, brothers, or sisters, persons in the same household living under similar conditions and

eating the same food, occurred from pernicious anemia or anemia. This may explain the family tendency to pernicious anemia in many cases.

REPORT OF CASES

Case A52257. Mr. W. T. L., aged forty-two years, a farmer for the past five years, came for examination April 26, 1911. The patient had had a spell of diarrhea for two months when working in a butter and cheese factory twelve years before. The diarrhea had recurred off and on until five years before, when it became more constant and severe; blood was passed at intervals. During the past one and one-half years the patient had lost 10 to 15 pounds in weight and had become weak and dyspneic on exertion. One year before sore mouth developed, at times severe enough to make eating difficult. During the past one and one-half months numbness and tingling had been noticed in the hands and feet.

Examination.—The examination of pus from around the teeth revealed many motile amebæ and two organisms from the flagellata, one evidently *Trichomonas*, the other narrower and much longer than *Trichomonas* and trichomonades. The total gastric acidity was 8; free hydrochloric acid 0. In the examination of the stool large numbers of *Balantidium coli*, but no amebæ were found. The blood picture is shown in Table 1.

Treatment.—Blaud's pills, Fowler's solution, and rectal injections of vinegar and tannic acid were given. For six months there were marked improvement and gain in weight with a great reduction in the number of *Balantidium coli* in the stools. Reexamination after nine months showed no *Balantidium coli* in one stool test, but the clinical symptoms and blood picture of pernicious anemia were still present.

Case A185278. Mr. G. A., aged thirty years, a farmer who had never been outside of Illinois, Minnesota, and Iowa came for examination February 9, 1917. The patient's father had died of pernicious anemia one year before. Nine years before and two years before, the patient had had short attacks of diarrhea. Five weeks before he had had "grippe" and one week later he had had a sudden attack of pain at the right costal margin running up into the chest and right shoulder, and difficult breathing. Diarrhea had been constant since the attack of grippe, with from four to five loose stools in the early morning and at night.

Examination.—The patient was pale and sallow. He had pyorrhea and much bridge work in his mouth. The systolic blood pressure was 116, the diastolic 54. The urine was negative for bile and urobilinogen, but urobilin was present. Roentgenograms of the chest and teeth were negative. The blood picture is shown in Table 1. The duodenal contents showed a brown trace of bilirubin, urobilinogen 1,000 units, and urobilin 1,400 units, indicating increased blood destruction. The examination of the central nervous system was negative. Six stool tests showed *Balantidium coli*, but no other parasites.

Treatment.—Thymol and Blaud's pills by mouth, and enemas of kerosene were given; in three weeks this eliminated almost all of the *Balantidium coli* and raised the hemoglobin from 30 to 70 per cent. The patient went home feeling much improved.

Examination six months later showed the *Balantidium coli* still in the stools, and the clinical picture and blood findings of pernicious anemia. Examination of the central nervous system showed the cord changes usually found in pernicious anemia. The patient was again treated with thymol, salol, Blaud's pills, and Fowler's solution, but he left for home after three weeks, unimproved. He died the following summer.

Case A215036. Mr. G. H. R., aged fifty-two years, a farmer, was examined November 26, 1917. The patient's father, brother, and sister died of similar trouble, "thin blood." For twenty years past the patient had had spells of pain in the upper abdomen lasting for

from one to two hours, with vomiting. He had had malaria at the age of fifteen. During the past year diarrhea had been persistent, five to six stools daily. He had lost about 60 pounds in weight; he had lost strength progressively, and in the past three months numbness over the entire body with tingling in the extremities had come on. His appetite was poor; he had not had a sore tongue. His memory had failed for two months and recently he had been irritable, and had had crying spells.

Examination.—The blood picture may be seen in Table 1. The systolic blood pressure was 150, the diastolic 100; the pulse 84. Examination of the urine was negative. The total gastric acidity was 10, free hydrochloric acid 0. Roentgenograms of the stomach were negative. Two blood Wassermann tests were negative. Proctoscopic examination showed very slight proctitis for 14 inches. The stool test revealed *Balantidium coli*, but no other parasite. Examination of the central nervous system showed subacute combined sclerosis.

Treatment.—The patient was treated for two months with thymol, chloroform, Bland's pills, and hydrochloric acid without improvement. *Balantidium coli* persisted in the stools, and the blood picture remained the same. The patient died two months after leaving the Clinic.

Case A21480. Mr. F. L. S., aged fifty-seven years, a farmer, was examined in the Clinic May 4, 1920. One sister had died of anemia at forty-eight. The patient had come to the Clinic eleven years before on account of weakness and loss of strength with spells of diarrhea, at times severe. One stool test had showed occult blood. The proctoscopic examination had been negative. During the following years the patient had had spells of diarrhea every ten days, lasting four or five days, with four or five watery stools a day, usually in the morning. Between attacks the stools were normal. Eight months before examination the patient had returned from the state fair with diarrhea and abdominal cramps. He noticed numbness in the extremities, his feet felt "asleep, or as if varnished," and he had some weakness of the anal and vesical sphincters.

Examination.—The patient's systolic blood pressure was 116, diastolic 78, and pulse 84. The test of the urine and the Wassermann test on the blood were negative. The total gastric acidity was 46, the free hydrochloric acid 0. Foci of infection were not found in the teeth or tonsils.

After tests on the stool and blood were made in the Clinic the patient went away for two days to visit relatives; he was brought back on a cot, with hemoglobin of 25 per cent.

Treatment.—The patient was treated with distilled chenopodium and he improved in every way. The number of *Balantidium coli* was greatly reduced. The patient was given enemas of vinegar and tannic acid every second day and arsphenamin intravenously once a week for five weeks. After the last treatment nine stool tests, August 5, 6, 12, 13, 19, and 20 and September 16, 17, and 18, failed to show *Balantidium coli*. The clinical symptoms of pernicious anemia are still present, and the last blood test, September 16, showed 55 per cent hemoglobin.

The examination of the central nervous system on three occasions is interesting in showing progressive involvement; May 11, when the hemoglobin was 30 per cent, the neurologist reported slight subacute combined sclerosis, hardly as extensive as in the average case of pernicious anemia of the same severity. July 14, the neurologist reported evidence to be insufficient for a diagnosis of a central nervous system lesion, but findings of combined sclerosis. August 21, the report was subacute combined sclerosis of the pernicious anemia type. This last report was made by a consultant who had not examined the patient previously.

TABLE 1
BLOOD FINDINGS IN FOUR PATIENTS HAVING BALANTIDIUM COLI

Case.....	A59257.		A189778.			A210386.		A21480.		
	4/26/11.	1/ 9/12.	2/19/17.	3/12/17.	9/28/17.	11/27/17.	12/21/17.	5/5/20.	5/19/20.	9/16/20.
Hemoglobin (per cent).....	35	43	35	70	40	44	48	25	59	55
Erythrocytes (millions).....	1.6	1.97	2.1	3.14	1.66	1.6	2.76	1.97	2.14	2.86
Color index.....	1.1	1.0+	0.8+	1.1+	1.2+	1.3+	0.8+	0.6+	0.9+	0.9+
Leukocytes.....	10,400	9,700	11,800	9,400	3,600	4,600	5,900	9,800	6,000	4,900
Cells counted.....	500	500	500	500	500	500	500	200	200	200
Polynuclear neutrophils.....	58.6	66.7	66.3	64.3	54.7	55.3	44.3	67.0	59.0	56.0
Small lymphocytes.....	32.4	29.0	26.0	29.3	37.7	33.7	45.3	29.0	53.0	58.0
Large lymphocytes.....	4.0	1.7	6.3	4.7	4.3	1.7	6.3	4.0	7.0	3.0
Eosinophils.....	5.0	1.7	1.3	1.7	2.7	8.7	3.7		0.5	2.0
Basophils.....		1.0			0.3	0.7	0.3		0.5	1.0
Neutrophilic myelocytes.....					0.3					
Normoblasts.....	4	1	1		8				1	
Megakaryoblasts.....	8									
Poikilocytosis.....	Marked.	Marked.	Moderate.	Moderate.	Marked.	Moderate.	Marked.	Moderate.	Moderate.	Moderate.
Granular degeneration of erythrocytes.....	Slight.		Moderate.	Slight.	Marked.	Moderate.	Moderate.	Moderate.	Slight.	Slight.
Polychromatophilia.....	Slight.		Moderate.		Slight.					Slight.

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THE RELATIONSHIP OF THE INCREASE IN BLOOD SUGAR CONCENTRATION TO THE CALORIGENIC ACTION OF GLUCOSE AND TO THE CALORIGENIC ACTION OF ADRENALIN*

WALTER M. BOOTHBY AND IRENE SANDIFORD

Forty-one experiments were made to determine the increase in the heat production, respiratory quotient, and blood sugar concentration following the ingestion of 100 gm. of glucose. Similarly, twenty-two experiments were done to determine the calorogenic action resulting from the subcutaneous injection of 0.5 c.c. of adrenalin chlorid. The majority of the patients had hyperthyroidism, although there was a sufficient number of nonhyperthyroid and of hypothyroid patients included to show that there was no consistent percentage difference in the reaction from the glucose or adrenalin caused by variable amounts of active thyroxin in the body.

Figure 214 shows the characteristic reaction produced by glucose and by adrenalin chlorid.

TABLE 1
AVERAGE RESULTS FOR TWO GROUPS OF EXPERIMENTS WITH GLUCOSE AND
ADRENALIN CHLORID

	Glucose.	Adrenalin.
Basal metabolic rate		
Before.....	+44	+34
After.....	+57	+62
Increase.....	13	28
Calories		
Percentage increase.....	9	20
Blood sugar		
Before.....	0.132	0.143
After.....	0.271	0.196
Increase.....	0.139	0.053
Percentage increase.....	101	37
Respiratory quotient		
Before.....	0.77	0.77
After.....	0.93	0.87
Increase.....	0.16	0.10

* Reprinted from the American Journal of Physiology, 1921, lv, 293.

The ingestion of glucose causes an increase in the heat production

Fig. 215.

Fig. 214.

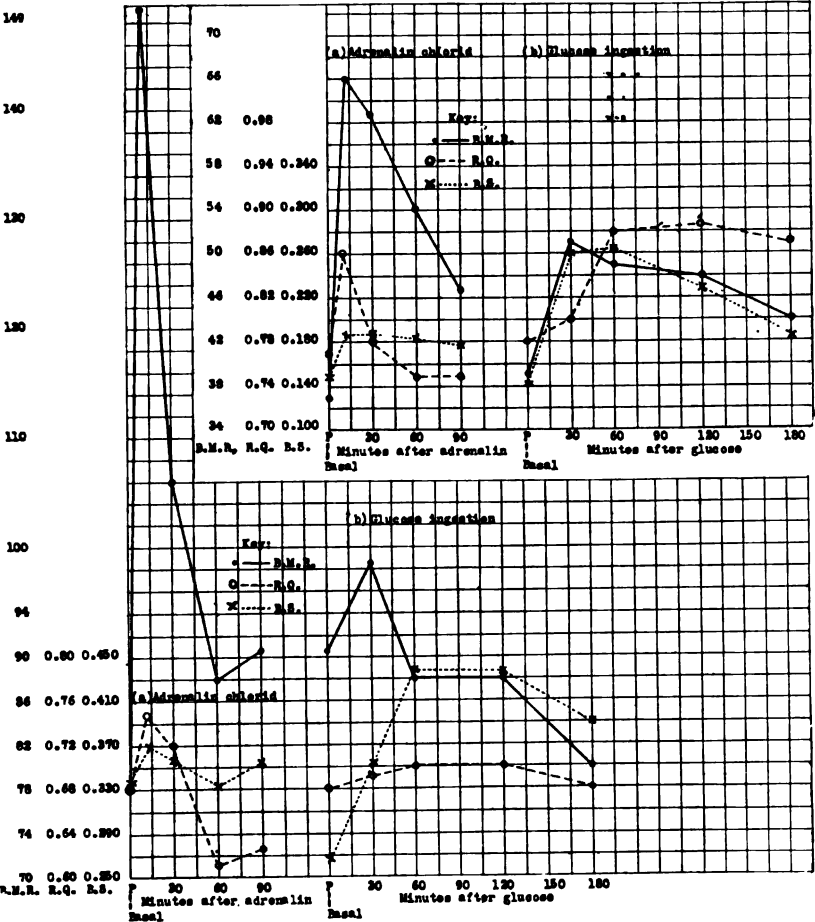


FIG. 214.—Increase in basal metabolic rate, respiratory quotient, and blood sugar: (a) After the injection of 0.5 c.c. adrenalin chlorid and (b) the injection of 100 gm. glucose (in 150 c.c. water) in a patient with moderate hyperthyroidism.

FIG. 215.—Increase in basal metabolic rate, respiratory quotient, and blood sugar: (a) After the injection of 0.5 c.c. adrenalin chlorid and (b) the injection of 100 gm. glucose (in 150 c.c. water) in a patient with marked hyperthyroidism complicated by a severe diabetes.

of 9 per cent for an increase in the blood sugar of 101 per cent; on the other hand, there is an increase in the heat production of 20 per cent as

a result of the injection of adrenalin chlorid with an increase of only 37 per cent in the blood sugar concentration.

These experiments are very strong evidence in favor of the theory tentatively suggested by us last year that adrenalin chlorid, at least in the quantity here given, has a calorogenic action on all the cells of the body, causing them to metabolize more rapidly. This calorogenic action is not due to the carbohydrate plethora coincidentally produced by the adrenalin as has been the previous general conception of the reaction. The mobilization of sugar is a most interesting compensatory mechanism to render available an abundance of ready fuel to satisfy the increased demand for it caused by the adrenalin. This assumption is further strengthened by the fact that adrenalin chlorid produced a very pronounced rise in heat production in an essentially complete diabetic patient (Fig. 215) with hyperthyroidism in whom the administration of glucose caused practically no increase in the heat production, although there was a very marked increase in the blood sugar concentration.

OBSERVATIONS ON GLYCEMIA, GLYCURESIS, AND WATER EXCRETION IN OBESITY*

CAROL BEELER AND REGINALD FITZ

Joslin has recently emphasized the fact that many diabetics are overweight for their age, sex, and height when the diagnosis of diabetes is first made, or have a history of obesity before they develop diabetic symptoms. It has seemed of interest, on this account, to observe the results of an alimentary glucose tolerance test in a series of nondiabetic obese patients in an attempt to determine how many had an abnormally low tolerance, and could, therefore, be classified on laboratory, as well as clinical evidence, as being prediabetic.

For this purpose a group of thirty-two stout persons was studied, consisting of eight men and twenty-four women who came to the Mayo Clinic for obesity or for obesity and some secondary ailment which could not definitely be related to diabetes. The urine of each patient was sugar free on routine examination.

One of the men weighed 370 pounds, one weighed 285 pounds, one 253 pounds, and the others were at least 10 per cent overweight for their age according to the Medico-actuarial statistics.² The heaviest woman weighed 291 pounds and several others weighed more than 225 pounds. The women, as well as the men, all weighed at least 10 per cent more than the normal for their respective ages.

The glucose tolerance test was conducted according to the plan of Hamman and Hirschman:

On the day of the test the patient ate no breakfast. A sample of blood and urine was obtained. The patient was given 100 gm. glucose in 500 c.c. lemonade. Samples of blood and urine were obtained thirty minutes later and one hour later. The patient was given 150 c.c. of water. Two hours later samples of blood and urine were obtained and the patient was given 150 c.c. of water. Three hours later final samples of blood and urine were obtained. Thus each patient drank 800 c.c. of fluid during the period of study and samples of blood were taken five times.

* Reprinted from the Archives of Internal Medicine, 1921, xxviii, 804-812.

The volume of each urine specimen was recorded and each was tested for sugar by Benedict's qualitative method. The blood sugar concentration was estimated by the method of Folin and Wu.

The observations on obese persons were controlled by similar tests made on ten nondiabetic patients of normal weight and on eleven mild diabetic patients. To the nondiabetic patients, however, 0.66 gm. glucose for each pound of body weight was given, and to the diabetic patients a routine dose of 50 gm. glucose instead of 100 gm. We were unable to graduate the dosage of glucose on the basis of body weight in the obese, as in the few cases tried such large doses as were necessary caused prompt nausea and vomiting. We did not feel justified in giving more than 50 gm. glucose to our diabetic patients, as their urines had

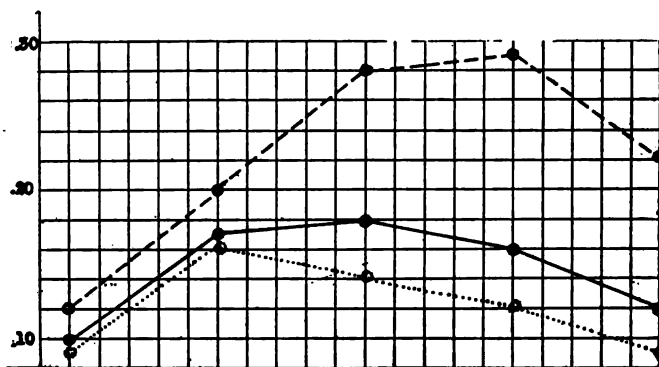


FIG. 216.—Blood sugar curve following the ingestion of glucose in nondiabetic patients, obese patients, and diabetic patients: Nondiabetic patients; obese patients; — — —, diabetic patients.

all been made sugar free before their sugar tolerance was tested in this fashion, and we were afraid that larger doses might be harmful.

Figure 216 shows composite curves of the blood sugar determinations in each of the three types of cases plotted by averaging all the results.

The average curve in the nondiabetic controls was not remarkable. The highest point in glycemia was reached shortly after the glucose was ingested, and such hyperglycemia as occurred disappeared so promptly that the last blood sugar reading was no higher than the first.

The average curve in the diabetic patients was also typical. The blood sugar reading did not reach its maximum and did not return to its original base line as rapidly as in normal patients, and its highest point was much higher than in the control curve.

The curve of the patients with obesity is more interesting. It appears to be midway between the normal and diabetic curves, although it approaches the normal shape more closely than the diabetic. It does not suggest that most of the persons in the series according to this test were prediabetic.

When the patients are considered separately, however, certain features are noteworthy. Four patients had a fasting blood sugar above 0.15 per cent. Two of these had a normal type of sugar curve in other respects. The other two gave a reaction to glucose so typical of diabetes as more positively to suggest that they represented an early stage

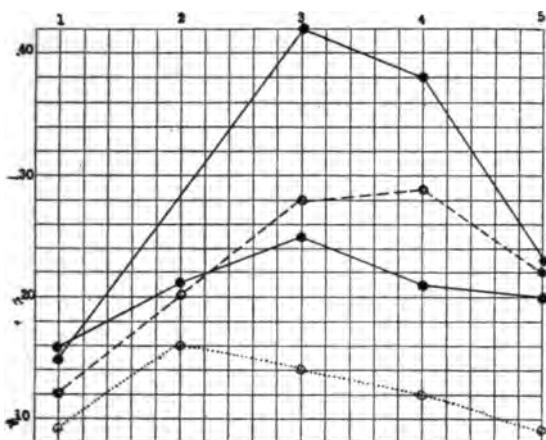


FIG. 217.—Blood sugar curve in two obese patients, suggesting early diabetes.

of the disease. The data from these two cases is shown graphically in Figure 217.

SYNOPSIS OF CASES

Case 1, a woman aged thirty-two years, 5 feet tall, had gradually gained from her normal weight of 120 pounds to her present weight of 164. She had no family history of diabetes or obesity. She came to the Clinic for the purpose of losing weight, and had no diabetic symptoms.

Case 2, a man aged forty-nine years, came to the Clinic because of palsy of cerebral origin; he had no diabetic symptoms except that he had lost 70 pounds in weight during the last fifteen months. His present weight was 196 pounds.

Six patients, while having a fasting blood sugar concentration of 0.12 per cent or less, had a persistent hyperglycemia following the ingestion of glucose and thus resembled mild diabetes in their type of reaction. The data from a marked example of this description are shown graphically in Figure 218.

Case 3. This patient was a short woman aged forty-one years, with incontinence due to a urethral stricture. She had gained 29 pounds in the last six months owing to physical inertia and excessive eating. She weighed 204 pounds.

On the whole, our results from blood sugar studies on obese patients with reference to the early diagnosis of diabetes mellitus were disappointing. The majority of the thirty-four patients observed had no fast-ing hyperglycemia and had a nearly normal blood sugar curve following the ingestion of 100 gm. of glucose. Marked deviations from normal, suggestive of diabetes, occurred in but few cases. There seemed little evidence for the belief that this test as performed was of marked clinical value except in rare instances. It is probable, however, that more striking results would be obtainable if the dosage of glucose were made on the basis of body weight and if the sugar solution were admin-

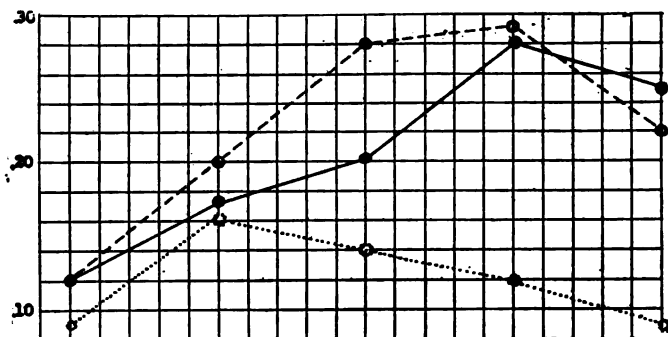


FIG. 218.—Blood sugar curve in one obese patient, suggesting early diabetes.

istered intravenously according to the method of Woodyatt, Sansum, and Wilder.

TABLE 1
EXCRETION OF SUGAR IN NONDIABETIC PATIENTS

Case.	Sex.	Age.	Weight, kg.	Total sugar excretion, mg.	Sugar, mg., for each kg.
1	F.	35	52.2	64	1.2
2	M.	42	69.5	154	1.0
3	M.	56	71.7	246	3.4
4	F.	18	54.5	467	8.6
Averages		38	62.0	233	3.8

Sugar excretion was estimated quantitatively in seventeen obese, four nondiabetic, and five diabetic patients. The total sugar elim-

inated after the sugar was ingested was determined by the method of Benedict, or of Benedict and Osterberg on the urine excreted during the period of observation.

TABLE 2
EXCRETION OF SUGAR IN DIABETIC PATIENTS

Case.	Sex.	Age.	Weight, kg.	Total sugar excretion, mg.	Sugar, mg., for each kg.
1	M.	48	76.8	2,165	28.1
2	M.	40	77.2	3,920	50.7
3	M.	55	91.0	5,500	60.5
4	M.	47	59.1	10,300	175.0
5	F.	20	43.6	12,092	275.0
Averages		40	69.5	6,795	97.8

TABLE 3
EXCRETION OF SUGAR IN OBESE PATIENTS
Part I

Case.	Sex.	Age.	Weight, kg.	Onset of obesity.	Total sugar excretion, mg.	Sugar, mg. for each kg.
1	F.	55	110.0	Gradual.	44	0.4
2	F.	39	87.4		106	1.2
3	F.	32	132.1		107	0.8
4	F.	21	109.0	34 kg. gain in one year.	138	1.3
5	F.	30	89.0	15 kg. gain in six months.	142	1.6
6	F.	54	79.5		146	1.8
7	M.	45	86.4		163	1.9
8	F.	62	91.0	Gradual.	211	2.3
9	F.	41	92.8	15 kg. gain in eight months.	314	3.4
10	F.	59	102.0	Gradual.	376	3.7
11	M.	52	168.0	Gradual.	428	2.6
Averages		44	104.0		198	1.9

Part II

1	F.	43	91.0	15 kg. gain in six months.	1019	11.2
2	M.	42	91.0	Gradual.	1208	13.3
3	F.	47	72.6	Gradual.	2794	38.4
4	F.	26	88.5	Gradual.	3737	42.2
5	M.	56	99.5	Gradual.	4950	49.5
6	F.	32	74.5	Gradual.	7850	105.3
Averages		40	86.0		3593	41.7

The amount of sugar excreted by the four nondiabetic patients varied between 64 and 467 mg., with an average of 233 mg. This, however, was in sharp contrast to the sugar excretion of the five diabetic patients who excreted much larger amounts.

The excretion of sugar by the obese patients was of two distinct types. Eleven patients excreted a normal or less than the average normal amount of sugar following the ingestion of 100 gm. of glucose, and six patients excreted an abnormally large amount.

With two exceptions all the patients who excreted small amounts of sugar in the urine had a normal glycemia curve. The two remaining patients both had a diabetic type of glycemia, so that in one the last sugar reading was 0.25 per cent and in the other the first and fifth samples were within normal limits, but the three middle specimens gave readings of 0.18, 0.23, and 0.22 per cent respectively. There was no evidence of any renal impermeability in these cases, though certain ones had symptomatic evidence of polyglandular insufficiency. These data are recorded in Part I of Table 3.

The fact that so many patients of this group excrete less than the average normal amounts of glucose after taking 100 gm. of pure sugar is noteworthy. It could be explained on the ground that the dose of sugar used per unit of body weight was small and that, therefore, the excretion of sugar was correspondingly small. On the other hand, the metabolism of obesity has received considerable investigation. Most authors follow von Noorden's classification of the two types of obesity. The first depends on a normal metabolism with adiposity developing through an increased food intake and a diminished energy expenditure. The second depends on a true slowing of metabolism. There is abundant evidence to explain the cause of the first type of case. There is less evidence in favor of the second. However, certain fat persons undoubtedly show a tendency to gain weight despite an intelligent regulation of diet and exercise, and others fail to lose weight when taking a low calory diet over a long period of time. These facts suggest an abnormal metabolism as the true cause of the condition.

Means recently investigated the basal metabolism in obesity using the Benedict apparatus and analyzing his data on the basis of the DuBois formula. He found no characteristic change in basal metabolism in the twelve cases which he studied, and he found that the specific dynamic action of protein was normal.

Waldvogel attempted to study one phase of fat metabolism in

obesity by injecting beta-oxybutyric acid subcutaneously and following its excretion in the urine and expired air. His evidence is not convincing, although his conclusions are interesting. He found a larger excretion of acetone in the expired air and urine of his obese patients than in control patients who had received the same dosage of acid and, therefore, believed that in adiposity there was some disturbance in intermediary fat metabolism by which beta-oxybutyric acid was not burned to its usual completion.

Wilder and Sansum reported on the sugar tolerance of a case of myxedema and five cases of hypophyseal disease which were studied by continuous intravenous injection. They found no increased tolerance in these cases by this method and concluded that the increased tolerance of such patients for sugar given by mouth is due to a retarded absorption from the bowel rather than to any anomaly of intermediate metabolism. These authors obtained the same results in a few cases of obesity studied at that time.

Some of our observations suggest, in spite of this evidence to the contrary, that certain obese patients may store sugar with abnormal ease or else burn it with unusual thoroughness. At least this explanation would account for our findings in those patients without evidence of renal impermeability, who excreted an abnormally small amount of sugar in the urine following the ingestion of glucose, and who must have absorbed the sugar from the stomach as was shown by the temporary rise in the concentration of circulating sugar. A reaction of this sort by sparing protein or fat metabolism might readily be a factor in the development of "endogenous" obesity. It requires more thorough investigation.

The observations on the patients who excreted abnormally large amounts of sugar following the ingestion of glucose are summarized in Part II of Table 3. All had a glycemia curve suggestive of mild diabetes. It would seem justifiable to believe that obese patients who respond to a standard dose of glucose by a curve of glycemia suggestive of diabetes, and by an increased total excretion of urinary sugar, should be treated at the outset for diabetes, as von Noorden found that of fifteen such patients whose course he followed for a long time, five were known to develop genuine diabetes later.

Several of our patients exhibited an interesting peculiarity in relation to the excretion of urine following the rapid intake of 800 c.c. of fluid. The nondiabetic controls excreted between 100 and 800 c.c.

of urine under these conditions, with an average excretion of 418 c.c. Of thirty obese patients, three excreted less than 100 c.c. of urine in the two hours' observation time, and only four excreted more than the average normal of 418 c.c. Of the seven diabetic patients, on the other hand, only two excreted less than 300 c.c. of urine in two hours, and the others excreted more than 500 c.c., so that the average of the group was 501 c.c. As a general rule obese patients with normal blood sugar curves and without an exaggerated glycosuria excreted small volumes of urine, while those with a diabetic curve of glycemia and with an increased excretion of sugar had a relatively large volume of urine. Such oliguria in obesity has been explained by Labbé and Furet on the basis of chlorid retention, and by Grafe, who found that interference with the water balance is not uncommon and is often dependent on interference with the thyroid mechanism for regulating intracellular water metabolism. The recent work of Larson, Weir, and Rowntree suggests that the pituitary gland as well may play a part in this mechanism.

CONCLUSIONS

Obese patients show characteristic changes in sugar and water metabolism which may be of importance in subsequent treatment. Certain patients show a relatively normal curve of glycemia following the ingestion of 100 gm. of glucose. These patients tend to excrete small volumes of urine and small quantities of sugar. They do not appear to retain sugar because of an impermeable kidney, but rather to have some disturbance in sugar and water metabolism which may be related to an endocrinopathy. It seems possible that these patients burn or store sugar with unusual rapidity, a reaction which may have a sparing influence on fat and protein metabolism and may be a factor in the development of adiposity. The effect of water retention in these patients is not known. They are probably not likely to develop subsequent diabetes, and should be treated for obesity and endocrin disease, if the existence is demonstrable.

On the other hand, another group of obese patients has a curve of glycemia following the ingestion of 100 gm. of glucose which resembles that of mild diabetes. These patients excrete abnormally large amounts of glucose in their urine over a measured interval of time and excrete normal amounts of urine or may even have a slight diuresis. This type of case probably represents early diabetes and should be treated accordingly.

The fasting blood sugar estimation or the glycemia curve alone is of little significance, and is probably of less importance than the determination of glycuresis.

A sugar tolerance test in obese patients which includes a blood sugar curve and quantitative measurement of sugar and fluid output affords valuable diagnostic and therapeutic information.

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PREOPERATIVE PREPARATION OF PATIENTS WITH OBSTRUCTIVE JAUNDICE*

WALTMAN WALTERS

The fact that jaundiced patients bleed too freely following operation has been known for several years, and in the absence of exact criteria many surgeons have looked for one or another clinical sign for an index to the severity of the operative risk. Some surgeons believe that purpuric spots on the patient with obstructive jaundice are advance agents of death in case of operation; others believe that a blood coagulation time of more than nine minutes is a contraindication to operation, and still others that dehydration with marked jaundice persisting more than two or three weeks is a contraindication. Further, there is no doubt that many cases of cholelithiasis and stones in the common duct have been diagnosed as malignant disease and the patients have been returned to a life of invalidism, since the surgeon did not wish to do an abdominal exploration because, in the presence of jaundice, it seemed to entail grave risk.

This study was made for the purpose of investigating the reason for the high mortality following operations on patients who have obstructive jaundice. The reports of patients from the records of the Mayo Clinic during 1918, 1919, and 1920 who had obstructive jaundice at the time of operation and who have died were reviewed in order to determine the cause of death and the relation of such cause to the degree of jaundice and the coagulation time of the venous blood. Only cases in which coagulation time estimations had been made were tabulated.

In Table 1 a comparison is shown between the findings at necropsy in twenty-nine patients with obstructive jaundice at the time of operation who died subsequently, and in thirty-four patients who were without jaundice at the time of operation who died. It is of interest to note that fifteen, more than 50 per cent, of the patients with jaundice died from intra-abdominal hemorrhage, or at least had a large amount of blood in the peritoneal cavity, while but 6 per cent of those without jaundice died from intra-abdominal hemorrhage.

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TABLE 1
FINDINGS AT NECROPSY IN PATIENTS OPERATED ON FOR LESIONS OF THE GALLBLADDER

	With jaundice.	Without jaundice.
Patients.....	29	34
Cause of death:		
Postoperative hemorrhage.....	16	2
Peritonitis.....	3	5
Bronchopneumonia.....	3	4
Pulmonary embolism.....	..	6
Cerebral embolism.....	..	1
Ileus.....	..	3

TABLE 2
FIFTEEN JAUNDICED PATIENTS DYING FROM POSTOPERATIVE (INTRA-ABDOMINAL) HEMORRHAGE

Case.	Age.	Degree of jaundice.	Degrees of bile.	Coagulation time, minutes.	Calcium time, minutes.	Operation.
A341399	39	4	1	10	10	Choledochotomy; cholecystectomy.
A255676	48	2		23	28	Choledochotomy; cholecystectomy.
*A209163	34	2	2	8		Dilatation of stricture; choledochotomy.
A210429	48	4	3	14.5		Choledochotomy.
A197147	37	4	4	13		Cholecystostomy.
A335927	50	3	2	15	11	Exploration.
A200538	43	3	2	8		Exploration.
A241960	53	2	2	20		Cholecystectomy; choledochotomy.
*A235723	48	4	3	16		Dilatation of stricture; choledochotomy.
A231348	64	2	1	10	12.5	Cholecystectomy; choledochotomy.
A226821	65	4	2	6	17	Cholecystostomy; choledochotomy.
*A262802	29	4	3	36	35	Dilatation of common duct.
A267424	57	3		10	9	Cholecystectomy. Removal of stones.
*A271933	39	4	2	17	14	Choledochotomy.
A328617	47	1	1	7.5		Cholecystectomy. Closure of gallbladder fistula.

* Coagulation time more than nine minutes in eleven of fifteen patients. In ten of fifteen patients the jaundice was graded 3 or 4.

Table 2 shows the degree of jaundice, coagulation time, and operative procedures on the fifteen jaundiced patients who died from postoperative hemorrhage. In eleven of the fifteen patients (73 per cent) the coagulation time was more than nine minutes. In ten (66 per cent) the jaundice was graded 3 or 4 on a scale of 1, 2, 3, 4.

It is noteworthy that in all cases death occurred from one to seven days after operation, as may be expected if continuous oozing is taking

place. If the cystic artery or one of its branches were the cause, death might be expected immediately following operation. At necropsy in every instance the exact source of the hemorrhage could not be found.

In order to determine whether deaths from hemorrhage were dependent on an elevated coagulation time and marked jaundice a study was made of the case histories of fourteen patients, the only patients in whom comparisons had been made of the coagulation time and degree of jaundice, who were jaundiced at the time of operation on the bile tract, and who died from causes other than postoperative abdominal hemorrhage. It was found that but three had had a coagulation time of more than nine minutes, and five, jaundice graded 3 or 4 (Table 3). Only two of the fourteen had had cholecystectomies, the others some type of drainage operation on the bile ducts.

TABLE 3
FOURTEEN JAUNDICED PATIENTS DYING FROM CAUSES OTHER THAN HEMORRHAGE

Case.	Degree of jaundice.	Degree of bile.	Coagulation time, minutes.	Calcium time, minutes.	Operation.	Cause of death.
A327611	2	2	5	8	Cholecystogastrostomy.	Suppression of urine.
A306039	4	3	6	9	Cholecystostomy; choledochotomy.	Bronchopneumonia.
A269833	3	Trace.	6		Transduodenal excision of carcinoma.	Peritonitis from rupture of incision.
A253416	1	1	10	12	Removal of specimen.	Bronchopneumonia.
A212281	1	2	5.5		Cholecystostomy; choledochotomy.	Peritonitis.
A183889	3+	4	12	20	Hepaticoduodenostomy; exploration of ducts.	Abscess of liver; purulent pericarditis.
A211383	1	1	11		Choledochotomy; exploration of common duct.	Thrombosis of portal vein; abscess of liver.
A199201	4	3	9	11	Choledochotomy.	Nephritis following transfusion from wrong donor.
A189394	2	2	6	8	Cholecystostomy.	Peritonitis.
A192733	3	2	8		Cholecystostomy; choledochotomy.	Tuberculosis; bronchopneumonia.
A24548	2	2	7		Cholecystostomy; choledochotomy.	Fat necrosis (?).
A214233	2	2	7		Cholecystostomy; choledochotomy.	Cholangitis.
A350691	1	0	7.5	4.5	Cholecystectomy.	Necrosis of the head of pancreas.
A352666	2	+	8		Cholecystostomy.	Questionable.

Coagulation time more than nine minutes in three of fourteen patients. In five of fourteen patients the jaundice was graded 3 or 4.

These facts presented in Tables 2 and 3 seem to be direct evidence that the cause of death of most of the patients with obstructive jaundice was postoperative intra-abdominal hemorrhage, which seemed to be due to a continual oozing from traumatized surfaces rather than bleeding from severed arteries. The corollary of this is that in deeply jaundiced patients the tissues should be handled with the utmost care and gentleness and oozing from the liver surface prevented by refraining from doing a cholecystectomy until the jaundice has subsided.

Two methods of determining the coagulation time of the blood are used in the Mayo Clinic, Boggs' method, in which estimation is made by the time required for blood from a stab wound in the ear to coagulate, and the method described by Lee and White, in which the coagulation time is determined by the time it takes for 1 c.c. of blood withdrawn from a vein to coagulate. The blood is withdrawn by a syringe and placed in a test tube, both having previously been washed with normal salt solution. The Lee and White method is preferred because in Boggs' method the true coagulation time of the blood is shortened by the combination of the juices of the tissues of the ear with the blood, as has been definitely shown by Lee and White. The test of the calcium time of the blood described by Lee and Vincent is also made in the Clinic. Six drops of a 0.5 per cent solution of calcium chlorid are added to 1 c.c. of venous blood, and the time required for the blood and the calcium chlorid to coagulate is called the calcium time of the blood. These observers have shown that when the calcium time is lower than the coagulation time of the blood the coagulation time in most instances can be lowered to approximate the calcium time by the administration of calcium lactate by mouth for a three-day period. They proved that a retarded coagulation time could be produced experimentally in dogs by producing an obstructive jaundice, and that this retardation of the coagulation time appeared at the end of the fifth week of the jaundice. They were able to produce an immediate reduction in the coagulation time of these animals by intravenous injections of 2 per cent calcium lactate, such reduction being sustained for from two to three days without deleterious effect on the general condition of the animals.

Besides lowering the coagulation time by calcium, some observers believe that calcium is beneficial in decreasing the toxemia of patients with obstructive jaundice. Among the most noteworthy theories is that of King and Stewart, who believe that bile pigments in combination with calcium or with sodium are less toxic than uncombined pig-

ments; they consider calcium a protective mechanism against circulating pigments of obstructive jaundice.

King, Bigelow, and Pearce conclude that obstructive jaundice produced in dogs results in a loss of calcium, the calcium being given up by the bone to neutralize the toxic bile pigments circulating in the blood and tissues. Such neutralization affords protection to the body, but may lead to secondary disturbances, for example, bradycardia and changes in the blood coagulation time. In view of the work of these investigators the belief seems justified that calcium offers the best means of preparing jaundiced patients for operation, since it not only

TABLE 4

THE EFFECT OF PREOPERATIVE PREPARATION ON THE COAGULATION TIME OF VENOUS BLOOD IN PATIENTS WITH OBSTRUCTIVE JAUNDICE

Case.	Age.	Degree of jaundice.	Degree of bile.	Coagulation time, minutes.	Calcium time, minutes.	Coagulation time after preparation, minutes.	Preparation.
A352536 H. H. E.	54	4	3	16	12	9.25	5 c.c. 10 per cent calcium chlorid intravenously daily, 3 days; 100 grains calcium lactate daily, 4 days; carbohydrate diet; 4000 c.c. water daily.
A339670 M.	53	3	3	14	9	2*	5 c.c. 10 per cent calcium chlorid intravenously daily, 2 days; 100 grains calcium lactate daily, 4 days; carbohydrate diet; 3 per cent glucose solution proctoclysis; 4000 c.c. water daily.
A353678 J. F. W.	55	4	2	16		5†	100 grains calcium lactate daily, 5 days; carbohydrate diet; 3 per cent glucose solution proctoclysis; 4000 c.c. water daily.
A357387 J. L. T.	60	4	4	12 (5/6/21)	12 (5/6/21)	6 (5/17/21)	5 c.c. 10 per cent calcium chlorid intravenously daily, 3 days; 100 grains calcium lactate daily, 5 days; 15 per cent glucose solution proctoclysis; 4000 c.c. water daily.
A357833 L. B.	46	4	4	5.5 (5/14/21)	5.5	4 (5/16/21)	5 c.c. 10 per cent. calcium lactate intravenously daily, 2 days; 100 grains calcium lactate daily, 4 days; glucose solution proctoclysis; 4000 c.c. water daily, 4 days.
A369429 C. C. T.‡	37	4	4	9	12	2	5 c.c. 10 per cent calcium chlorid intravenously, daily for 3 days; 10 per cent glucose solution proctoclysis; 4000 c.c. water daily; carbohydrate diet.
A286431 F. F.	50	4	4	6	2	2	5 c.c. 10 per cent calcium chlorid intravenously, daily for 3 days; 10 per cent glucose proctoclysis; 4000 c.c. water daily; carbohydrate diet.

* Twenty-two days after operation the coagulation time was five minutes and fifteen seconds. The jaundice was greatly decreased.

† Fifteen days after operation coagulation time was three minutes, forty seconds; marked diminution in jaundice. Thirty days after operation coagulation time was five and one-half minutes.

‡ Patient had bleeding gums, petechia, and subcutaneous hemorrhages which began to disappear after the intravenous injections of calcium, and did not reappear.

reduces the coagulation time of the blood but also decreases the toxemia produced by the circulating bile pigments. We have adopted the suggestion of Lee and Vincent to use calcium intravenously. From 5 to 10 c.c. of a 10 per cent solution of calcium chlorid in redistilled water, which was given each of six patients with obstructive jaundice who had abnormally high blood coagulation times, lowered the coagulation time to normal after three injections on successive days. In addition, four of these patients were given calcium lactate by mouth in doses of 100 grains daily (Table 4).

Recently Grove and Vines have stated that they have proved experimentally that calcium salts given by mouth have no influence on the blood calcium, in which case the administration of calcium intravenously is the method of choice, since the calcium not only lowers the coagulation time of the blood but also combines with the bile pigments circulating in the blood stream.

That the intravenous injection of calcium in small doses is not a harmful procedure has been proved (Lee and Vincent). Cambell has given calcium acetyl salicylate to fifty-five patients in doses of 0.5 gm. in 10 c.c. of distilled water (a concentration similar to our calcium chlorid solution) at three-day intervals, in some cases as many as seven injections for relief of neuralgias and myalgias. This emphasizes the fact that calcium in small doses may be given intravenously without deleterious effect. I have given 10 c.c. of calcium chlorid in 10 per cent solution and 10 c.c. of calcium lactate in 10 per cent. solution separately to two pregnant dogs over a seven-day period without any apparent ill effect. During the course of these injections both dogs delivered several living puppies.

The intravenous injections of calcium chlorid in patients have been supplemented by doses of calcium by mouth, although Cushny says, "The small quantity of calcium absorbed from the alimentary canal has no obvious effects." This statement does not always hold good, since some reduction in an elevated coagulation time can be brought about by the administration of calcium lactate by mouth, although, inasmuch as it does not increase the amount of calcium in the blood stream (Grove and Vines), and hence does not combine with the bile pigments circulating in the blood, it does not diminish the patient's toxemia and consequently its value is 50 per cent less than the intravenous administration of calcium. Furthermore, the calcium administered by mouth was found by Lee and Vincent to have little effect in lowering an elevated

blood coagulation time until after the third day, while the effect of the intravenous administration of calcium is noticed immediately. This is illustrated in Case A353678 (Table 4). The patient showed a reduction in coagulation time to normal after the oral administration of 100 grains calcium lactate daily for five days.

It should be borne in mind that "calcium injected directly into the blood stream acts much like digitalis in that in small doses it accelerates and strengthens the heart, but in large doses it seems to be poisonous, tending to bring the heart to a standstill" (Cushny). In our investigations daily injections of 10 c.c. of 10 per cent calcium lactate and 10 per cent calcium chlorid were given for a seven-day period without apparent deleterious effect on dogs, and since a maximum of three injections of 5 c.c. of 10 per cent calcium chlorid has sufficed to produce a prompt immediate and sustained reduction of the coagulation time the intravenous use of the calcium chlorid solution in preparing jaundiced patients seems justifiable.

The duration of the reduction in coagulation time for each injection of calcium lactate was found by Lee and Vincent to be three days. In our cases we have not definitely determined this point, a study of which will be made later. However, in one case the reduction remained for fourteen days, in another eight days. When the coagulation time tended to lengthen we found that it could be immediately reduced by another intravenous injection of the calcium chlorid solution.

Opie, from his experimental work, believes that carbohydrates act in a protective manner to prevent disintegration of the body proteins when the individual is in a state of toxemia; he found that on giving carbohydrates, fats, and proteins to dogs before and after chloroform poisoning, the dogs that were fed with fat died first, those fed with protein died second, and those fed with carbohydrate died third or not at all. Mann has been able to keep dogs alive for from twenty to thirty-four hours after the removal of the liver by intravenous, subcutaneous, and intraduodenal injections of glucose. In view of this work jaundiced patients in the Clinic have been fed large quantities of carbohydrates, and the amount of glucose has been increased by using the Murphy drip proctoclysis of 15 per cent glucose solution in tap-water, one hour on and one hour off. Four thousand cubic centimeters of water were given by mouth every twenty-four hours to increase the body fluids and to aid in the elimination of the bile pigments. Attempts have not been made to carry on these preparations longer than four days, because it

is believed that this length of time will give the maximum benefit, and that waiting longer might invite another attack of colic if gallstones are the cause of the biliary obstruction, which would deepen the jaundice and increase the coagulation time. If the patient does not respond to this régime transfusion of blood is indicated twenty-four to forty-eight hours before operation. In this manner we have prepared for operation fifteen patients with obstructive jaundice, most of whom would otherwise have been denied operation because of the grave risk due to their elevated coagulation time, dehydration, and toxemia. All of these patients recovered from the operation and were able to return home.

The facts brought out in the study of these cases are illustrated by Case A339670.

Mrs. M., aged fifty-six years, gave a history of increasing jaundice over a period of twenty-four months with marked loss of weight and strength. She had had severe abdominal colic often. The large liver and the fluctuating abdomen led several physicians to believe that the bile ducts and liver were malignant. When her coagulation time was reported to be fourteen minutes, it was thought that the operative risk was too great, particularly since the symptoms were 75 per cent in favor of malignancy. The conditions were explained to her, but she refused to leave the Clinic without an operation. She was, therefore, prepared for operation in the manner described and her coagulation time reduced from fourteen minutes to two minutes in four days. At operation stones in the common duct and secondary biliary cirrhosis were found. There was no evidence of malignancy. The patient recovered, and was dismissed from the Clinic twenty-eight days later.

CONCLUSIONS

1. Most patients with obstructive jaundice who die after operation succumb from intra-abdominal hemorrhage.

2. In most cases postoperative hemorrhage occurs when the coagulation time of the venous blood is longer than nine minutes.

3. The coagulation time of the blood can be reduced greatly and the toxemia diminished in patients with obstructive jaundice by daily intravenous injections of 5 c.c. of a 10 per cent calcium chlorid solution for a three-day period.

4. Carbohydrates and glucose prevent disintegration of body proteins when the patient is in a state of toxemia.

5. Large quantities of water aid in eliminating toxic bile pigments and increase the body fluids.

6. It is self-evident that in operations for obstructive jaundice the various steps of the operation should be carried out with the utmost gentleness, care being taken not to traumatize the tissues, especially

of the liver, and for this reason cholecystectomy should not be performed at the primary operation if it can be avoided.

I wish to express my thanks to Dr. L. F. Bell for many valuable suggestions received from him and from his thesis "Degeneration and regeneration of the liver during experimentally produced obstructive jaundice" (unpublished).

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JAUNDICE FROM PANCREATIC DISEASE*

CHARLES H. MAYO

In considering jaundice due to pancreatic disease the cases of so-called hemolytic jaundice caused by blood cell pigment stain, a chronic condition in which the spleen is a factor, and the large percentage of cases of jaundice in which the gallbladder is small and there are stones in the common duct, so well described by Courvoisier, are eliminated at once, even though the pancreas may be secondarily involved. Facts relating to the mechanics of jaundice may be stated briefly. Bile is formed in the liver and should pass freely through the hepatic duct and the common duct into the intestine. The common and hepatic ducts are joined at their juncture by the cystic duct from the gallbladder, an added reservoir, which normally contains about 1 ounce, although it is capable of distention, should occasion require, to a capacity of several ounces. Just why man and some animals have gallbladders and others do not is problematic, since the exact function of the organ is not yet known. Part of its function evidently is to maintain the stability of tension in the ducts under which the liver secretes bile and protects itself by the exudate of mucus from its lining. Experimentally, bile from the hepatic duct injected into the pancreatic duct is more irritating than bile from the gallbladder.

In nature no duct delivers directly into a viscus, but by sigmoid bends or by passing for a space between the mucous membrane and muscular layers of the viscus so that internal compression may block from backflow, while it interferes but little with delivery. It is worthy of note that all tubes or ducts at the point of delivery are closed by muscle rings, while long tubes like the alimentary canal are encircled at each change in structure by automatic muscle rings. Practically all ducts and tubes deliver intermittently through the stimulus of content.

In jaundice, bile in the blood causes staining of the skin, conjunctivæ, and tissues, as well as of the urine and unnatural fluids, although the

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secretion of mucus, milk, and saliva is not affected. The degree of jaundice is comparable with the degree of obstruction. In a study of the manner of the entrance of bile into the blood Saunders and others experimentally caused jaundice by ligating the common duct of animals, but when the chyle duct is ligated first, lymphatic absorption and delivery into the blood are blocked and jaundice does not develop. The absorption of bile depends on the presence of lymphatics in the liver, gallbladder, and ducts, and on the pressure or tension. Any cause which interferes with the delivery of bile into the intestine can cause jaundice, for example: absorption of bile in the liver as a whole or in its parts, caused by new growths, the development of connective tissue with atrophy, cysts, or the obstruction of ducts from within by inflammatory and temporary swelling of mucous linings as the result of infection, cholangitis, or from acute or chronic diseases, or definite infections, such as malaria, yellow fever, acute yellow atrophy, and toxic jaundice in general; also from within by concretions and parasites, and by direct closure from external pressure by enlarged glands or new growths. Anatomically, the common duct grooves the head of the pancreas; it penetrates the outer wall of the duodenum, passes indirectly through the muscle and between muscle and mucous membrane for a short distance, and, just before delivering into the free cavity of the bowel, unites, as a rule, with the pancreatic duct of Wirsung; the secretions from the gallbladder and the pancreas pass through the one outlet.

The area of the pancreas grooved by the common duct is covered by the duodenum by a more or less intimate attachment extending over one-third of the duodenal circumference. The important feature of this association of ducts is its variability; thus the pancreas may open through the same papilla and the duct be completely separated to the outlet, or the two ducts may unite for a considerable distance as one duct. The two ducts, the pancreatic and biliary, may have separate openings, as in many of the lower animals. The usually larger duct of Wirsung may be the smaller, and the duct of Santorini opening between the pylorus and the common duct may be the larger. The two pancreatic ducts may not communicate in the head or in the body of the gland. In considering the relationship between the function of the liver and the delivery of bile in association with the function of the pancreas and the delivery of its secretion, is it possible that the union of the two ducts renders the pancreas more vulnerable to secondary infection following

infection of the gallbladder and ducts? The function of the liver is essential; man could live but a few hours without it. Bile is a byproduct of great value of the liver function; probably it provides the system, by way of the intestine, with a constant immunity against the temporary dangers that may arise from food and its accidental toxins. It emulsifies fats, lubricates the intestine, and favors peristalsis; its presence is noted by the color it gives the stool. We have observed several cases of jaundice for from many months to several years, in which there was no bile in the intestine; the retention then of bile is of itself not a cause of death. We have observed the delivery of all the bile to the surface through a fistula for many months or several years; its retention or

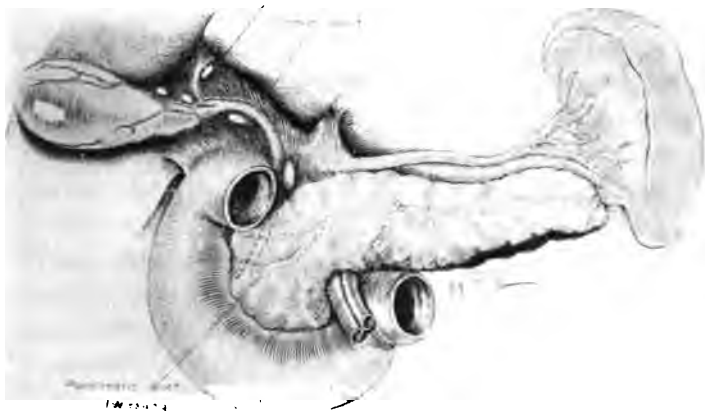


FIG. 219.—Distribution of lymph nodes along the course of the cystic, hepatic, and common ducts.

delivery into the intestine therefore is not necessary to life, notwithstanding that such conditions cause serious discomfort.

The condition or conditions which cause jaundice are of great importance in determining methods of treatment and prognosis. Inasmuch as the pancreas partially or completely surrounds the common duct, any case of jaundice, until differentiated, may be considered as possibly caused by the constriction of the latter. Temporary inflammation, sclerosis, and chronic disease, or new growths may be the cause. In a fairly high percentage of cases the pancreas is involved by varying degrees of inflammation associated with infection of the gallbladder and ducts; such a condition and the size of the lymphatic

glands and the common duct should be recorded in all cases of operation on the gallbladder and duct for future reference in case of recurrence of the disease.

The pancreatic secretion is of far greater importance than bile from a digestive standpoint, and two ducts are provided for its delivery. It is evident from reviewing the diseases of the pancreas and the surgical procedures developed for their relief that a small part of the normal secretion is sufficient as a hormone or activating agent to give very satisfactory digestive results. Within the pancreas are those very important areas of tissue, the islands of Langerhans, which largely control carbohydrate metabolism. Inflammation of the pancreas is not uncommon; it should undoubtedly be considered a chemical change caused by toxemia from alimentary intake in acute conditions, while subacute and chronic inflammations, which also are chemical in their effect on the tissue, should be looked on as the result of microbic action. From my experience in operations on the gallbladder and ducts and examinations of the pancreas I believe that most of the chronic diseases of the pancreas and a few of the acute diseases are secondary to infections of the gallbladder and ducts, and that a small group of cases of serious acute and chronic infections which cause symptoms do not follow primary gallbladder disease, but that the conditions are reversed.

Disease of the gallbladder is now generally admitted to be the result of chronic infection of its tissues, with possibly, but not necessarily, some secondary infection of its contents. The empyema of total cystic duct obstruction is not caused by the same germs that caused the original cholecystitis. The former conception of infection of the bile and then of the gallbladder from infection reversed through the common duct, or the lymphatics, or the portal circulation by way of the liver, is less plausible than that infection is a direct result of attack through the blood by microbic infarctions in the capillaries. While it is admittedly possible that the pancreas can be involved secondarily through the duct association, especially if bile can enter the pancreatic duct, it is more probable, according to modern investigations of routes of infection, that it also occurs through the blood. The more diseased the gallbladder is found to be on exploration, the less is the probability that the pancreas is the cause of the trouble, and if it is involved the involvement is secondary; the reverse is true with great distention of the gallbladder and an unobstructed cystic duct. The usual types of pancreatitis are: (1) the intralobular, in which the inflammatory process

chiefly involves the outer part of the lobules, causing a lumpy irregular enlargement of the head or of all of the gland, and only in gross disease involving the islands of Langerhans; (2) interacinar pancreatitis in which the surface is smoother and the enlargement of the gland greater, and in which the diffuse inflammation more often involves the islands of Langerhans and is more commonly associated with glycosuria (the latter type often produces abscesses, and not infrequently is seen with fat necrosis); and (3) hemorrhagic pancreatitis which occurs as an acute condition of the abdomen, associated with acute inflammation of the gallbladder and ducts with acute jaundice, but it is a secondary disease from bile in the pancreatic ducts, apparently rendering parts of the gland subject to autodigestion. The pain in some cases of so-called gallbladder disease may be attributed in part to pancreatic disease as certain characteristics of pain from pancreatic colic are noted in the absence of the gallbladder and without obstruction to the flow of bile. Inflammation of the pancreas may occur with dull pain more or less constant in the region of the pancreas, usually attributed to the stomach; the pain is deep, extending to the spine; it may be to the right of the midline in the region of the gallbladder, as well as to the left in the region of the body and tail of the pancreas. With pain may occur an intermittent diarrhea and loss of weight, followed later by jaundice, or jaundice may appear early in a rapidly progressing case; it is probable that in such cases the common duct deeply grooves the pancreas, favoring early obstruction. Such variations of symptoms are noted with cancer of the pancreas.

A large cystic gallbladder with the stone blocking the cystic duct and protruding through and blocking the common duct is a rare but possible finding on exploration, and is one of the few exceptions (Courvoisier) from the usual small gallbladder noted in cases of common duct stone. The result of obstruction of the common duct from the pancreas, aside from jaundice, is pain, indigestion, loss of weight and strength, and occasionally diabetes. The stools are light colored from lack of bile or from the presence of an excess of undigested fats. Chills and fever are not the rule, as with infection and gallstones. Physical examination in the early or acute condition usually reveals but little; later an indefinite sense of a deep tumor mass may be felt and often a round tumor to the right of the midline is noted which is probably the distended gallbladder; the liver is enlarged and, if irregular and lumpy, is probably involved by metastasis.

Cancer of the pancreas is usually not rapid in its progress; it extends over many months, and in the early stage jaundice may vary in intensity as bile passes through the duct from time to time.

In milder cases of chronic pancreatitis there is some difference of opinion as to whether the gallbladder should be removed or drained for a long period. Mann's research work shows that removal of the gallbladder greatly lowers the tension within the duct, reducing the spastic closure of the sphincter of Oddi. External drainage of the gallbladder for a period of many weeks may be justified in certain inflammatory conditions of the pancreas. These conditions but rarely cause jaundice for more than a brief period and of mild degree. However, admitting the difficulty of diagnosis, the greatly distended gallbladder with jaundice in middle or old age is more probably associated with malignant disease of the pancreas and many of the symptoms of discomfort are due to the jaundice, the itching, the blood changes, and the loss of bile from the alimentary tract. In such cases cholecystoduodenostomy or cholecystogastrostomy, according to the ease and safety in which either may be made, the former generally being preferable, short-circuits the delivery of bile, gives great relief, and undoubtedly prolongs life. The operation is not advised at a time when hemorrhagic ecchymosis from intense jaundice is noted over the body. Some patients with greatly delayed coagulation time of the blood require special preparation and calcium treatment for a prolonged period, and possibly blood transfusions before and after operation in order to control the serious complication of hemorrhage which may even occur from the nose and mucous membrane of the alimentary tract. The fistulous opening remains patent only when the obstruction of the common duct is complete and permanent. The relief is most marked in inflammatory disease, and yet life is greatly prolonged and rendered more comfortable in cases of cancer of the pancreas.

PERNICIOUS ANEMIA WITH SPECIAL REFERENCE TO THE SPLEEN AND THE LARGE INTESTINE*

WILLIAM J. MAYO

Pernicious anemia is characterized by progressive degeneration of the red blood cells, permanent change in the method of the production of blood, marked changes in the spinal cord, achlorhydria, and glossitis. The relation of the cord changes, achlorhydria, and glossitis to the anemia has not been determined. The view held formerly, that the conditions were dependent on the anemia, is scarcely borne out by the fact that the symptoms are found in the earlier stages of the disease, neurologic examination showing that the cord changes may be as characteristic at any stage of the disease as the blood picture. The etiology of pernicious anemia is unknown, the early symptoms are indefinite, and by the time a diagnosis can be established the condition is incurable.

It has been asserted that certain cells found in the blood of patients with pernicious anemia are characteristic, but most observers agree that the pathologic change is in the blood as a whole, rather than in the development of specific types of blood cells. While it is known that the actual perversion of the red cell formation lies in the bone marrow, few believe that the cause originates therein. One might say that the bone marrow of a patient who has died from pernicious anemia furnishes only presumptive evidence of the disease. The pathologist would indeed be enthusiastic who asserted that in anemia other than of the aplastic type he could make a diagnosis of pernicious anemia from the bone marrow examination alone. The diagnosis of pernicious anemia is by no means certain in the early stages. Most diagnosticians have had under their care patients believed to have pernicious anemia in the early stages who recovered with or without treatment. All have seen patients in whom the disease was so insidious in

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its manifestations that it had reached the incurable stage before its existence was suspected. Giffin, Woltman, and Szlapka now have under observation a number of cases in which there are achlorhydria and some evidences of changes in the cord and tongue, but as yet without anemia. It will be interesting to learn in what percentage, if any, of these cases pernicious anemia develops.

THE RELATION OF THE SPLEEN TO PERNICIOUS ANEMIA

The relation of the spleen to the formation of the blood led the earliest observers of pernicious anemia to suspect that the spleen was associated with the disease. It remained for Eppinger to suggest that the removal of the spleen might cure, and early reports give testimony of temporary relief after splenectomy sufficient to justify a fair trial of the operation. Considering the confusion which so often attends the early diagnosis, it seems probable that obscure cases of hemolytic icterus and splenic anemia may have been accidentally included in the pernicious anemia group, especially since the pathologic changes in the spleen in pernicious anemia are not characteristic of the disease. Removal of the spleen in such cases has possibly given the impression that splenectomy may cure pernicious anemia. It has been a tradition of the medical profession that recovery of a patient in the face of a diagnosis of pernicious anemia proves the diagnosis wrong, and this conviction is still so strong as to prevent our readily accepting reports of cures. Even a superficial examination of the literature on pernicious anemia brings out in striking manner the fact that any form of treatment for pernicious anemia may be beneficial, or at least may appear to be beneficial. Patients with pernicious anemia have their ups and downs, and in an occasional case in which the diagnosis seemed to have been established by physicians of repute, there has been recovery which has lasted for years. Eppinger's work at least demonstrated that the removal of the spleen initiated striking temporary improvement. In the cases observed in the Clinic there was marked gain in weight, and improvement in hemoglobin on an average of from 36 to 72 per cent, and the red-cell count increased on the average from less than 2,000,000 to more than 4,000,000.

Previous to November 1, 1917, fifty splenectomies had been performed in the Clinic for definitely established pernicious anemia. The operation was then discontinued almost entirely for three and one-

half years. Since there was not sufficient evidence that splenectomy would cure these patients, and since at that time the procedure was not known to give a degree of palliation sufficiently greater than that following blood transfusion, it seemed wise to await the verdict of time. Giffin and Szlapka have recently investigated the condition of these fifty splenectomized patients, and the pessimism which existed in the Clinic has been partly dispelled at least. It was found that 21.3 per cent of the patients with pernicious anemia survived the operation three years or more, living two and one-half times as long as the average in a similar group of nonsplenectomized patients at the same stage of the disease, and that 10.6 per cent are alive after more than five years. This clearly indicates in at least one-third of the cases that the average life of patients with pernicious anemia is greatly prolonged and in about 10 per cent the prolongation is sufficient to lead to the hope that cures may result in some cases. We must take into consideration too the fact that no allowance was made for the normal mortality for the age period; all the patients who died were considered to have died from pernicious anemia. In the literature I have not found a comparable group of nonsplenectomized pernicious anemia patients who have done as well. The results in these fifty patients have been much better than we expected they would be when we abandoned the operation; they suggest that in certain early cases, of a type as yet not fully recognized, splenectomy offers a possibility of cure. Not only is this true but also in the average cases the palliation following splenectomy is much greater than we have been able to obtain by blood transfusions. Transfusion gives temporary benefit. It seems to furnish red cells which may live and function for one or two months or more, but there is not as yet evidence that the actual prolongation of life by that means is considerable. The blood picture improves after splenectomy, but the achlorhydria continues and careful examination of the nervous system does not show changes for the better in the physical condition of the nerve structure, although the patients are much better in this respect clinically. A perhaps comparable showing was made by Stokes in the Clinic, who found that careful treatment in syphilis of the nervous system made 86 per cent of the patients self-supporting, although the neurologists on examination were not able to find that there had been any marked change in the physical condition of the nervous system. Perhaps a lesion in the spinal cord gives physically the same signs whether the process is active

or whether it is the scar of a former lesion. Clinically an ulcerating syphilitic lesion of the skin is more troublesome than the scar of a healed lesion.

The course of pernicious anemia following splenectomy, generally speaking, is ameliorated, the relapses are less severe, and the cord changes less rapid than after transfusion or any other form of treatment with which we are acquainted. One of the functions of the spleen is to destroy deteriorated red cells. Apparently in pernicious anemia the red cells are born feeble and the spleen sacrifices red cells which, although imperfect, are the best the patient can produce and are capable of function. Removal of the spleen stops this destruction, but does not greatly affect the disease otherwise. The cases which seem to be most favorable are those in which hemolysis is most active, and those least characteristic of the disease. It also seems certain that early cases give a better prospect of benefit than late cases. When the disease has advanced to the point at which the bone marrow has been injured beyond the power of recuperation the most to be expected is a temporary abatement of the symptoms.

Pathologic examination of the spleens we have removed has been rather disappointing. If we might assert that in the cases of pernicious anemia in which splenectomy was performed characteristic pathologic changes are found in the spleen, or that greater clinical improvement followed splenectomy in pernicious anemia when the spleen was greatly enlarged, we could establish a definite relationship between the enlarged spleen and the disease, but the size of the spleen did not seem to bear any definite relationship to the severity of the disease. Necropsies after death from pernicious anemia have often shown the spleen to be small, but during the life of the patient the spleen is usually enlarged. The average weight of the spleens removed in our cases was 400 gm. (195 gm. normal, Sappey) exclusive of two large spleens, one of which weighed 1,600 gm., and the other 2,220 gm. It seems probable, therefore, that during the course of pernicious anemia the spleen is enlarged, but that this enlargement is reduced to a certain extent in the terminal stages of the disease. The spleens removed during the earlier stages of the disease, therefore, would show an average greater weight and size than would be found at necropsy. In only two of our cases (both terminal) was the spleen below normal size. In pernicious anemia of the aplastic type the changes in the bone marrow are most marked and the spleen small. Whether this has any significance I do not know.

The question is not yet answered whether pernicious anemia is a definite entity or whether it is a terminal change of several conditions, and recognizable as pernicious anemia only when the patient has reached the state which we know will eventuate in death. If we assume that the removal of the spleen has a beneficial effect, as appears from the evidence at hand, are we to assume also that the spleen is the cause of the changes in the bone marrow? A study of the literature and of our cases does not give this impression. It would be more reasonable to assume that the same agents which destroy the bone marrow injure the spinal cord, produce the achlorhydria and the glossitis, and affect the spleen and that by removal of the spleen a vicious circle is interrupted.

The operation of splenectomy for pernicious anemia is simple. Among the first nineteen patients we had three deaths. The patients were operated on during crises as a last resort in very advanced cases. The best plan is to transfuse once or twice in order to get the patient on the up grade before operating and not to operate during a crisis. We have had no operative deaths in the last forty cases.

THE POSSIBLE RELATION OF THE LARGE INTESTINE TO PERNICIOUS ANEMIA

Many observers have expressed the belief that toxic materials from the gastro-intestinal canal are the cause of pernicious anemia, and if this is true the probable location of this absorption would be in the proximal half of the large intestine. In a former communication* I discussed the physiology and pathology of the right half of the large intestine, my interest being excited primarily by the frequency of surgical tuberculosis and carcinoma of the large intestine, and still further by the work of Lane on intestinal stasis, which, like Banquo's ghost, will not down. There is a mystery concerning this portion of the human anatomy which conceals some queer metabolic disturbances, possibly, as I pointed out before, the result of throwing protein end products, which quickly undergo putrefactive changes, into an organ like the proximal absorbing half of the colon which primarily has an herbivorous function. Carcinoma or tuberculosis of the proximal half of the large intestine produces an anemia, unexplained by hemorrhage,

* Mayo, W. J.: Resection of the first portion of the large intestine and the resulting effect on its function. Jour. Am. Med. Assn., 1914, lxiii, 446-449.

much more severe than the anemias of carcinoma or tuberculosis of any other part of the body. Carcinoma of the fundus of the stomach perhaps is the only condition which produces an unexplained anemia which is in any way comparable. Tumors in the right half of the colon which are curable by operation may cause a reduction of the hemoglobin to below 25 per cent, edema of the lower extremities, and a general physical condition which would apparently place the patient beyond surgical interference. Experience with a large number of resections for the relief of such patients in wretched general condition has shown a comparatively low mortality and a high percentage of permanent cures.

The flaw in Lane's assumption that the colon is the source of toxins is the failure to find evidences of disease on removal of the colon, beyond adhesions, dilatation, and atony. Yet the same is true of exophthalmic goiter; the thyroid tissue of the hyperthyroidism is, strictly speaking, not so much abnormal as hypertrophied and superactive.

Some very interesting observations on *Balantidium coli* as the cause of blood and cord changes of the pernicious anemia type have been made by Logan, of the Clinic, and, in a way, the cases studied support the hypothesis of the intestinal origin of pernicious anemia. The *Balantidium coli* is a flagellate parasite which rarely inhabits the intestinal tract of man, but is common in the pig. In man it is found in the intestinal wall, the blood vessels, and other organs; it has the power of encysting and produces ulcers. The symptoms and findings of pernicious anemia or of an anemia which cannot be distinguished from it accompany the chronic type of the infection. Eosinophilia is not present in the chronic cases. Glaessner has found a hemolytic agent in *Balantidium coli*. Since this parasite penetrates the intestinal wall and its blood vessels and other organs of the body, and encysts, it is impossible to be sure that the organism is not harbored in the tissues of the body simply because it has been eradicated so that it is no longer found in the stools. Thus, if the pernicious anemia syndrome persists it cannot be determined whether the *Balantidium coli* hemolysin is still active, or whether once the complex is started it becomes an entity. In any event the pernicious anemia of *Balantidium coli* progresses to a fatal issue. The number of observed cases is small and the pernicious anemia might have been a coincidence. Honest card players have been known to hold four aces.

I fully realize that there is little evidence to show that the etiologic

agents of pernicious anemia arise in the large intestine. Pernicious anemia annually destroys more than 6,000 lives in the United States. Even though the disease is common, we have learned comparatively little concerning it during the past generation. It behooves us to keep an open mind, to study carefully the blood conditions of all patients who have disease of the large intestine, to try to ascertain whether anemia, achlorhydria, glossitis, or some other abnormal condition exists, and especially to study carefully all cases in relation to cause and effect in which the large intestine is removed or in which splenectomy is performed.

SPLENECTOMY IN SPLENIC ANEMIA AND BANTI'S DISEASE*

WILLIAM J. MAYO

Splenic anemia is characterized by an enlarged adherent spleen, a secondary type of anemia, and leukopenia. The etiology of splenic anemia is unknown; rather, let us say, if we know the cause the condition is not called splenic anemia, but is considered part of the disease of which it is one of the manifestations. This syndrome in children was described by Gretscl, in 1866, and various observers had called attention to sporadic cases; not until the publication of Osler's paper, in 1900, however, was the attention of the American medical profession drawn to the disease, and our knowledge of it may be said to date from that time.

While splenic anemia has quiescent periods, it eventually terminates in death, often from an intercurrent malady which the condition invites. The anemia is subject to considerable variation. When extreme, it is usually the result of intercurrent gastric hemorrhages. Leukopenia is a rather constant feature; the white cell count is usually well under 5,000, the average being 3,500, although occasionally it is much higher. We have operated on several patients in whom the white cell count had run rather steadily above 10,000. Pathologically the spleen shows generalized fibrosis and thrombophlebitis with atrophy of the pulp cells.

In 1883, Banti described an enlargement of the spleen associated with portal cirrhosis of the liver. He believed that the changes in the spleen, which consisted of a gradual conversion of the parenchyma into fibrous tissue with atrophy of the cellular elements and degeneration of the blood vessels, were the result of an infection. The fact that an unknown cause is essential to the diagnosis at once shows the lack of essentials in Banti's understanding of the subject. Most observers are now of the opinion that Banti's disease is merely a late stage of

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splenic anemia, presuming that the etiologic agents which are removed by the spleen from the blood stream affect not only the spleen but also terminally the liver. As we discover one by one the various initiating causes of these changes in the spleen the number of cases of Banti's syndrome is reduced. Banti not only laid stress on unknown etiology but also on the terminal changes in the liver. It may be stated, however, that the type of cirrhosis produced is portal, showing that the cause of the disturbance is carried to the liver through the portal vein. The evidence at hand leads to the belief that both the anemia and the cirrhosis of the liver are the result of the pathologic condition of the spleen, rather than of toxic material supposedly removed from the blood, and that the exciting cause of the splenomegalia may have little to do with the changes in the blood and liver. As there is enlargement of the spleen in many cases of primary cirrhosis of the liver, there is need for more accurate observation in order to clear up points which must otherwise be conjectural. At the present we may argue that if the discovery of an enlarged spleen is made first, and of the portal cirrhosis later, the condition is splenic anemia. On the contrary, if there is a history of alcoholism or pepper addiction and the condition of the liver is noticed first and that of the spleen later, we may say that the trouble is primary in the liver and that the splenomegalia is secondary to the liver changes. In the two extremes this method of classification will answer clinically, but unfortunately in many instances the history and physical findings are confusing and indeterminate.

Warthin and Dock have made careful observations in some cases of splenomegalia of the splenic anemia type which had progressed to the secondary condition with the changes in the liver described by Banti. In the cases presented by them are splenic fibrosis, hepatic cirrhosis, stenosis, and calcification of the portal system, causing passive venous chronic congestion and hyperplasia of the hemolymph nodes which are closely associated in function with the spleen. Warthin and Dock lay great stress on thrombophlebitis and believe that the generalized thrombosis is secondary to portal thrombophlebitis and that this condition itself is the result of chronic infection. Warthin summarized the findings thus: "Splenic anemia and Banti's disease must be regarded as coördinated symptom-complexes and not individual disease entities," a statement with which I quite agree.

The spleen is enlarged in cases of biliary cirrhosis also, especially in the mixed forms. I have been impressed with the futility of the mor-

phologic classification of the hepatic cirrhoses. There are many cirrhotic pictures, just as there are many patterns of wallpaper or carpets. Brushing aside the familiar classification of the cirrhoses of the liver in which variations in the morphology lead to unnecessary confusion, there are fundamentally but two hepatic cirrhoses:

1. Portal cirrhosis, in which the toxic material reaches the liver by way of the portal vein and in which the connective tissue is deposited around its branches. Death is caused by portal circulatory obstructions, ascites, and gastro-intestinal hemorrhages without jaundice until shortly before death.

2. Biliary cirrhosis, caused by infection of the biliary ducts in which the connective tissue is deposited around the ducts and causes jaundice, but without ascites or hemorrhages until shortly before death.

We understand best the atrophic type of portal cirrhosis of Laennec, but there are many cases, probably half or more, in which the liver is typically cirrhotic, is not decreased in size, but is even increased, as seen in the beer-drinker's liver in contradistinction to the hob-nail, or gin livers. While the liver in portal cirrhosis may be large or small, it usually is rough; at times, however, deposits of fat smooth out the surface roughness and lead to confusion of type.

REDUCTION OF THE PORTAL CIRCULATION BY SPLENECTOMY

In portal cirrhosis the spleen may play a prominent part in the etiology, and splenectomy in properly selected cases may be of great benefit. By splenectomy not only the supply of toxic material, if there be such, is cut off from the general circulation, but also the portal blood stream is reduced by subtraction of the amount of blood poured into the portal vein from the spleen, about 25 per cent of the total under normal conditions. After the removal of some of these huge spleens an enormous reduction of the portal circulation takes place, so that the hepatic cells may be relieved of a sufficient overload to enable them to function normally, and, moreover, the liver under favorable circumstances has the power of regeneration. Our experience with portal cirrhosis of the liver secondary to splenic anemia encouraged us to remove the spleen in some cases of primary portal cirrhosis. In all, eleven patients with portal cirrhosis were subjected to splenectomy with four deaths in the hospital. All of these patients were in the last stages with ascites, hemorrhage from the stomach, and so forth. Only in such grave cases did we consider the operation justi-

fiable. After removal of the spleen the omentum was spread in the denuded splenic area and fastened in the abdominal wound in order to give the additional benefits of the omentopexy of Talma-Morison and Drummond, which we have occasionally found of great benefit in relieving the ascites and other evidences of portal obstruction. Four of these patients were markedly benefited. One patient is now alive after five years. In early operations the operative mortality would be small and the end-results much better.

Biliary cirrhosis, usually of the obstruction type of Adami, must be considered in this connection. As pointed out, the connective tissue in this disease is deposited around the biliary ducts from infection, commonly from the extension upward of common duct infections from gallbladder disease. Infection from obstruction pancreatitis extending to the biliary ducts is also an occasional source of biliary cirrhosis. Sometimes the infection of the duct is focal in origin, and is carried to the biliary channels by the blood stream. The biliary cirrhosis may be complicated by portal cirrhosis, perhaps secondary to the pathologic condition of the spleen which has been caused by, or is a part of, the primary biliary cirrhosis. It is difficult in some cases of biliary cirrhosis to exclude latent hemolytic icterus as a contributing factor. In twenty of thirty-two cases of hemolytic icterus in which we performed splenectomy gallstones were present, usually bile-pigment stones the result of the enormous amount of pigments derived from the unnecessary red blood cell destruction in the spleen. Splenectomy was performed in six cases of primary biliary cirrhosis with greatly enlarged spleens. In these cases the cause of the biliary infection, so far as could be learned, had been removed previously, such as gallstones and focal infections, without marked relief. All of the five patients who recovered were greatly benefited, three are alive two years, two, three years, and one five years after splenectomy.

Hemorrhage from the stomach, so disturbing a feature of splenic anemia, is not always relieved by splenectomy, but is greatly reduced in frequency, and the majority of the patients never have hemorrhage after splenectomy. There are two known causes for hemorrhage of the stomach in these cases, first, esophageal and gastric varicosities, the result of portal obstruction, and second, toxic conditions, undoubtedly hepatic in origin, which result in extensive superficial gastric mucous erosions of the Dieulafoy type. The prospects of relief by splenectomy, however, depend not only on whether the spleen is the

primary cause, but especially on the condition of the liver. We have seen patients with very advanced cirrhosis of the liver who have been relieved of the ascites and gastric hemorrhages and have recovered marvelously after removal of the spleen. In one such case the patient, a physician, operated on by C. H. Mayo, had what appeared to be a terminal condition of splenomegalia and hepatic cirrhosis. He is well and in active pursuit of his profession more than eleven years after splenectomy. Balfour, in an article on gastric hemorrhages of splenic origin, reports in detail a case in which the removal of a moderately enlarged spleen checked gastric hemorrhages of many years' duration from which the patient was almost exsanguinated. Five previous operations of various kinds had failed to cure. The patient has remained well for more than four years. We have since had a similar experience. Sherren, Cushing, and others have called attention to the fact that after removal of the spleen for splenic anemia an occasional patient has a recurrence of hemorrhages. Of our seventy-one patients splenectomized for splenic anemia, eight died from gastro-intestinal hemorrhage during the next ten years. As Balfour points out, the hemorrhages are often the result of toxic substances produced in the liver, and the removal of the spleen will not always restore the liver to normal.

SPLENECTOMIES

Up to January 1, 1921, 249 spleens were removed in the Clinic for all causes, with a mortality of 10+ per cent.

Splenic anemia.—Of the 249 splenectomies, seventy-one were for splenic anemia of unknown origin, with nine deaths. In addition, splenectomy was performed in thirty-eight cases for splenic anemias of known origin. These cases deserve some attention.

Chronic sepsis.—We have removed eleven spleens which had become greatly enlarged in the course of chronic general sepsis following septic arthritis, tonsillitis, phlebitis, and osteomyelitis, with three deaths in the hospital. The other patients were cured or greatly benefited.

Syphilis.—Splenomegalia is often found with chronic syphilis, especially in the cases in which thorough treatment fails to maintain a negative Wassermann reaction. Some observers who have had wide experience with syphilis have believed that the large majority of cases of so-called splenic anemia are syphilitic in origin. In the syphilitic spleen generalized fibrosis and thrombophlebitis are found as well as

specific changes, especially modified forms of gumma; frequently the *Spirochæta pallida* can be demonstrated. We have removed the spleen in six cases of this kind, with one death in the hospital. Patients who had resisted thorough syphilitic treatment, and in whom chronic anemia was a manifest sign, were at once made amenable to treatment and quickly recovered.

Characteristic portal cirrhosis of the liver may be an end-result of syphilis, and finally death results from circulatory obstruction, ascites, hemorrhage from the stomach, and so forth, quite like the other cases of splenic anemia.

Splenic anemia in children and von Jaksch's disease.—Von Jaksch has described an enlargement of the spleen in infants due to malnutrition which usually disappears on proper feeding, but some of these patients do not get well and the enlarged spleen and chronic anemia are carried into early childhood. We have removed eight spleens in such children without an operative death, and when the condition has not been too advanced cure has followed. The spleens removed have shown the characteristic generalized fibrosis and thrombophlebitis.

Malarial spleen.—Chronic malaria results in a splenomegalia with generalized fibrosis and thrombophlebitis that we recognize as a form of splenic anemia; ultimately some of the patients develop cirrhosis of the liver, ascites, hemorrhage from the stomach, and the characteristics described by Banti. The removal of the greatly enlarged spleen of this type relieves the anemia. The experience of Jonnesco in Roumania and Mourdas in Russia, as well as that of other observers, has shown that the malarial treatment becomes much more effective and that patients who were apparently incurable have been restored to health following splenectomy. The mortality has been considerable following splenectomy in these cases, but this is also true of the entire group of splenic anemias since the spleen is often adherent and may require unusual skill and care for safe removal. This is shown by the mortality in our series, which was much higher than that in any of the other pathologic conditions for which the spleen was removed. It is understood, of course, that the removal of the spleen does not cure the malaria, but removes a very serious complication which is one of the means by which the death of the patient is brought about.

Chronic splenomegalia.—Finally, there is a type of chronic splenomegalia, more common in women than in men, which exists for years without great detriment to the patient beyond the weight of the en-

larged spleen. In the cases that I have observed, however, chronic anemia has eventually developed, and in a few in which I have operated I have found the definite changes characteristic of splenic anemia. I think we must conclude that all such cases are quiescent types of splenic anemia. The confused state of our knowledge at least brings one thought to mind, that the patient with an enlarged spleen should be looked on as potentially ill, and unless the cause can be shown and relieved, splenectomy may be considered. There is no sharp dividing line between these cases and certain varieties of benign tumors, splenic apoplexy, and cystic disease without traumatism in which a definite pathologic condition exists in the blood vessels and may give rise to acute conditions such as intraperitoneal rupture of the spleen.

The mortality and end-results are satisfactory, considering the nature and condition of the patients subjected to operation. All of the patients we operated on were otherwise incurable and progressing to a fatal issue. The death rate from splenectomy in such cases will be high, and not all patients who recover will be greatly benefited. The later in the course of the disease the splenectomy is performed, the closer terminal and incurable conditions will be found. How can we expect to cure all the pathologic conditions found at necropsy? We cannot turn back the hand of time in disease, but early operation will give a low mortality and cure a higher percentage of patients than has been cured in the group which I have considered here.

TECHNIC OF OPERATION

In performing splenectomy in the Clinic the technic of Balfour is employed. The patient is placed on a table tilted slightly to the right. The midline incision of Ochsner and Percy is employed. It gives ready access to the spleen and permits necessary operative procedures on the gallbladder and appendix, and makes it possible to remove a specimen of the liver for microscopic examination. The spleen is rapidly loosened manually from its attachments to the diaphragm and to the outer parietes. It is drawn down into the abdomen, and the space is packed with a large, warm, moist gauze compress. While the spleen is retained in the abdomen to act as a barrier against the intestinal protrusion, the vascular connections between the spleen and the stomach are ligated, care being taken not to injure the stomach, which happened in two cases in our experience, one patient dying as the result of septic leakage. The inferior margin of the spleen is tilted out of the abdominal

incision and the attachments at the splenic flexure of the colon detached and ligated. The spleen is then lifted out of the abdomen and the omental and peritoneal attachments anteriorly are divided with a sharp knife, inspected, tied, and separated, exposing the vascular pedicle accurately. The spleen is turned partly turtle in order to expose the pancreatic notch of the spleen on the outer aspect of the pedicle, and the tail of the pancreas is freed. The splenic pedicle is then grasped in such a manner as to compress the artery between the thumb and the finger and is held during a few heart-beats in order to allow the venous blood to drain from the spleen back into the general circulation. Two forceps are then placed on the proximal side, and one next the spleen, and the pedicle is divided. A catgut tie is made in the groove of the deeper forceps as they are removed, and a second tie in the groove of the second forceps as they are removed. With fine catgut on a needle the separated peritoneal tissues and other loose tissues along the upper surface of the pancreas are drawn together and some small bleeding vessels in that situation are secured. The pack is then removed. As a rule there will be but little hemorrhage of the deeper attachments. Occasionally, however, there is bleeding; the catgut suturing should then be carried down through these spaces in a snaking stitch in order to compress the bleeding points which usually cannot be caught in this deep situation and tied separately. Care should be taken in coming to the diaphragm not to tear a hole through into the pericardium or pleura, an accident which happened in one of our cases, fortunately without bad result. If the needle is caught in the bleeding tissues on the under surface of the diaphragm with about 15 cm. of catgut slack in the fingers the needle may be allowed to pass up with the diaphragm on expiration and be caught as it comes back during inspiration.

SKIN AND SYPHILIS

THE PREVENTION OF ACUTE ARSPHENAMIN REACTION BY ANTIANAPHYLAXIS AND ATROPIN*

GEORGE J. BUSMAN

The acute nitritoid or anaphylactoid reaction and the late gastrointestinal upset following the intravenous administration of arspenamin are familiar to those of the profession whose scope of practice includes this form of medication. By the former term is meant the suffusion of the face, choking, and cardiorespiratory symptoms occurring immediately on injection, and by the latter, persistent severe vomiting with or without diarrhea, beginning some hours after injection. To those who insist on hospitalization of the patient for from six to twenty-four hours after treatment the occasional reaction in the average case may be of little significance. For the average practitioner, however, or out-patient clinics where hospitalization is not practical, even a mild reaction may be of considerable annoyance. Both reactions, on the other hand, may form a critical complication in those patients whose idiosyncrasy prevents even the absolutely necessary minimal use of the drug. The method described by Stokes provides a means of dealing with this situation which is simple and applicable to the large majority of cases.

Among various means that have been suggested for the control of the nitritoid or anaphylactoid reaction to intravenous administration of arspenamin, mention must be made of (1) special care in the preparation of the patient (fasting), (2) caution in alkalization of arsephanmin solutions (to prevent precipitation in the blood stream), (3) epinephrin solution (Milian) in from 5 to 15 minim doses as a means of controlling the reaction after it develops, and (4) epinephrin as a prophylactic (Berman). Our experience confirms the value of the first three. The employment of atropin and the induction of antianaphylaxis, suggested by Stokes, is of the greatest value, not as a routine, but as a means of dealing with the difficult case.

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The induction of antianaphylaxis, to which for convenience the term "Besredka technic" is here applied, is accomplished on the service of the Section on Dermatology and Syphilology by dividing the individual dose of arsphenamin into two portions, a small preliminary injection, one-tenth of the total amount of the drug being given one hour before the subsequent larger portion. Atropin when used alone is given hypodermically in one-fiftieth grain doses twenty minutes before the intravenous administration of the arsphenamin. Strickler has stated that the latter method is not effective, but it should be noted that he employed only one-seventy-fifth grain doses, whereas Stokes in his description of the method called attention to the need for one-fiftieth grain doses, and to the ineffectiveness of one-seventy-fifth grain. Occasional patients respond to the smaller doses, and not all are protected by one-fiftieth grain, which is the highest dose we have given. In some patients who are apparently highly reactive to arsphenamin, a combination of the two methods may completely inhibit a reaction when either method alone has failed to produce the desired effect. In combining the two methods a small "vaccinating portion" of the arsphenamin solution (one-tenth the total dose) is injected intravenously; twenty minutes later one-fiftieth grain of atropin is given hypodermically, and twenty minutes after the administration of the atropin the remaining or larger portion of the arsphenamin solution is injected. By the use of these methods we have practically eliminated the reaction in the treatment of susceptible patients, and patients who have been reluctant to submit to further injections have been induced to continue their treatment.

The cause of the nitritoid reaction has been a matter for much study and conflicting opinion. The true relation to anaphylaxis of the acute or nitritoid reaction and the later gastro-intestinal reaction produced by arsphenamin has not been established. Support for the belief that some such relation exists rests on more than mere clinical analogies. The supporters¹⁶ of the older humeral, or chemical, theory of anaphylaxis contend that the anaphylactic reaction is an intoxication brought about by the toxic substances elaborated in the blood stream of the sensitized animal as a result of interaction between antigen and antibody. The latter supposedly is of the nature of an enzyme, the poison being produced by the digestive action of the proteolytic enzyme (antibody) on the injected antigen. According to this theory a preliminary or sensitizing injection is necessary. Swift early showed with respect to

arsphenamin that such preliminary injection might not be necessary. Swift did show, however, that guinea pigs could be passively sensitized to a mixture of guinea pig serum and arsphenamin, and would on subsequent injection develop a true anaphylactic response.

By the newer conception of the physical mechanism of anaphylactic shock as developed in the American literature, especially by Jobling and Petersen, and by Novy and De Kruif,^{8, 9} it is contended that the proteins of the serum of the sensitized animal, rather than the injected antigen, are the source of the anaphylatoxin. In other words, the anaphylactic shock is produced by a change in dispersion of the colloids of the blood stream. The production of anaphylatoxin can, therefore, occur following the injection of colloidal suspensions, such as agar, or of inert substances, such as kaolin. Jobling and Petersen and Novy and De Kruif suggest that the reaction is analogous to the catalytic change of fibrinogen into fibrin in coagulation. The development of this theory has of course eliminated the objection to Swift's explanation.

MacKee, Stokes, and others have pointed out that the reaction observed following intravenous injection of arsphenamin in acid solution resembles the nitritoid crisis and anaphylactic shock and is proportional in severity to the rate of administration, that is, to the rate of precipitation of the drug in the blood stream. Danysz has maintained that the arsphenamin solution is essentially colloidal and that even when properly alkalized it is precipitated on its injection by the constituents of the blood plasma, and then formed again into soluble organic derivatives. The rate of this precipitation is dependent to some extent on the alkalinity of the solution and on the peculiarities of the blood plasma.

Hirano suggests that the reaction may occur from peculiarities of the individual blood plasma. He conceived the idea that there might be some intimate relation between arsphenamin and the suprarenal system in the development of anaphylactic shock because of the fact that epinephrin had been employed successfully in the treatment of this reaction. Hirano observed also that the development of a nitritoid crisis was successfully prevented by the administration of a dose of arsphenamin in two portions. He was able to ascertain by experiments in rabbits that there was some change in the chromaffin substance of the adrenal glands following the administration of arsphenamin. The inability to detect epinephrin in the blood plasma in appreciable amounts makes it debatable whether or not the reaction is due to

decrease in epinephrin in the blood of sensitized patients. It is conceivable, however, that a change of this nature in the blood plasma may have some effect on the precipitation of the colloidal solution of properly alkalized arsphenamin solution.

Schamberg, Kolmer, Raiziss, and Weiss, after a careful study of reactions to arsphenamin, concluded that the acute reactions to arsphenamin are due at least in part to traces of an unidentified impurity in the drug which for purposes of convenience they designate as substance "X." They¹¹ fail to support the observations of Danysz on the precipitation of properly alkalized solutions (disodium salt) in the blood stream.

Since certain sensitized persons react severely while other persons who receive the intravenous injection from the same solution prepared at the same time from the same lot of the drug, or even from the same ampule, remain unaffected, it is not improbable that the reaction involves an anaphylactic element and possibly the effect of an impurity in the drug. The protection of the patient by measures known to afford protection against anaphylactic shock as here described supports the theory of anaphylaxis.

In an examination of the records of the Section on Dermatology and Syphilology with reference to arsphenamin reactions, thirty-six cases were found in which the recurrence of arsphenamin reactions, of both the nitritoid and gastro-intestinal types, was so persistent that it was impossible to ascribe it to incidental or temporary fluctuations in the technic. Our technic of administration is quite constant and conforms in general to Public Health Service standards. The rate of administration of 1 dg. for each minute and the degree of dilution (20 c.c. for each decigram) has been found by prolonged experience to be entirely safe and reactionless for the majority of patients. In general, the patients have been under hospital observation for from six to twenty-four hours following each injection.

Of the thirty-six patients whose complete records of preoperative preparation and postoperative reactions are available, twenty-one evidenced their idiosyncrasy by repeated nitritoid reactions to successive injections. Fifteen patients had repeated attacks of severe nausea and vomiting from two to six hours after each injection. Since the preparation of the patient and the brand of the drug were identical for all patients it seems reasonable to assume that both types of reaction were the result of personal idiosyncrasies to arsphenamin. A reaction

to the first injection did not once occur. The average occurrence of the first reaction of the series was with the fifth injection, which thus suggests that the cumulative effect of repeated injections is able to produce idiosyncrasy in certain cases. That this acquired idiosyncrasy persists for some time is shown by the fact that on resuming treatment following a rest period of several months the patients usually exhibited the same tendency to react to the arsphenamin.

It is interesting here to recall the observation of Stuart and Maynard, on a cutaneous test for arsphenamin sensitization in patients who have developed toxic eruptions following treatment with the drug. These authors noted that the sensitiveness finally disappeared (thirty-six weeks in their case).

The observations here described seem to show that repeated anaphylactoid shocks and late gastro-intestinal reactions are often encountered in the same patient and that both types of reactions are controlled by the use of atropin or by the Besredka technic. The late gastro-intestinal reaction may bear a closer relation to the nitritoid reaction than at first appears. The combination of acute nitritoid crisis and late gastro-intestinal reaction was observed in eight patients in this series. The following case is an example of such a combination.

REPORT OF CASES

Case 1 (A321202). Miss S., a robust woman, aged twenty-seven years, was under treatment because of a positive serum Wassermann reaction on the blood. Her only general complaint was chronic attacks of mild appendicitis. The patient was receiving intravenous injections of arsphenamin (arsenobenzol) in doses of 0.3, 0.4, and 0.4 gm. at weekly intervals. Immediately following the fourth injection (the previous doses had been 0.3, 0.4, and 0.4 gm.) she developed typical acute nitritoid crisis. This reaction was readily controlled by the subcutaneous administration of ten minims of 1 : 1,000 epinephrin solution. One week later she exhibited the same reaction following her treatment. Her sixth injection was given in two portions (Besredka technic). Reaction did not occur. The patient was then placed on a three months' rest period with interim inunction treatment. On resuming the arsphenamin treatment she showed no untoward effect from the first two injections. Four hours after the third injection, however, a severe gastro-intestinal disturbance developed, consisting of persistent nausea and vomiting for several hours. She reacted similarly a week later. Following her next (fifth) intravenous injection she experienced both a nitritoid crisis and subsequent nausea and vomiting. For her last treatment arsphenamin was administered in two portions. Reaction did not occur.

Another case is reported which illustrates the relation between the gastro-intestinal reaction and the nitritoid crisis, as well as the dosage of atropin indicated:

Case 2 (A203427). Miss P., a well-developed girl of twenty-one years, complained of stiffness of the extremities. She had an evident inherited syphilitic infection with a positive blood Wassermann reaction. She received five injections of arsphenamin (arsenobenzol) at weekly intervals, the dosage ranging from 2 to 4 dg. No reaction resulted dur-

ing the course. Four months later following each of three consecutive weekly injections the patient experienced severe nausea and vomiting. With the next two injections, an acute nitritoid crisis and a late gastro-intestinal reaction occurred. On the resumption of arsphenamin injections three months later one-one-hundred-fiftieth grain of atropin was administered hypodermically twenty minutes before injection. There was no reaction. Nausea and vomiting followed the arsphenamin injection a week later, however, even though the preliminary injection of atropin (one-one-hundred fiftieth grain) had been given, and one-one-hundred-fiftieth grain of atropin given hypodermically before the next injection failed to prevent an acute nitritoid crisis and late gastro-intestinal reaction. One-fiftieth grain of atropin was given before the next and last injection. No reaction resulted.

In order to show how treatment may be continued in a highly susceptible patient by the use of atropin, or the Besredka technic, or by a combination of both, another case is cited:

Case 3 (A261250). Mr. M., a large healthy appearing man, aged thirty-one years, was under treatment for central nervous system syphilis. He experienced no reaction to the first four injections of arsphenamin at weekly intervals. Following the fifth and sixth injections, however, acute nitritoid crises occurred. After three months' rest with interim mercurialization reactions did not occur following the first two arsphenamin injections, but an acute nitritoid crisis followed the third injection. By the use of the Besredka technic reaction did not develop following four subsequent injections of arsphenamin. With his sixth injection, however, a mild reaction resulted, even though the injection was given in two portions. Following another rest period of four months, the patient still presented the same idiosyncrasy to arsphenamin as shown by a severe nitritoid reaction after the first injection. One-fiftieth grain of atropin did not entirely prevent reaction to his second injection, which was followed by a slight flush. A combination of the Besredka technic and atropin (one-one-hundred-fiftieth grain), however, completely prevented any reaction to four subsequent arsphenamin injections in this course and to four similar injections during a course of treatment three months later.

SUMMARY

1. The exact nature of nitritoid and gastro-intestinal reactions to arsphenamin is undetermined. It seems not improbable that a variety of causes may act to produce a single syndrome of which the acute reaction on the table, and in certain cases the late gastro-intestinal reaction, may be phases of the same phenomenon.

2. In the group of cases herein reported, repeated nitritoid crises associated with repeated gastro-intestinal reaction persisted regardless of any controllable factor in the technic.

3. Repeated uncontrollable acute reactions are interpreted as personal idiosyncrasies of the patient to the drug.

4. The observation of Stokes on the value of atropin and of induced antianaphylaxis (Besredka technic) in the control of a persistent tendency to acute nitritoid crisis is confirmed.

5. It has been further found that a tendency to repeated late gastro-intestinal reaction can also be controlled in a large number of cases by either method alone, or by a combination of the two methods.

6. Atropin is sometimes effective in doses less than one-fiftieth grain. It may fail entirely to affect reaction even in doses of one-fiftieth grain.

7. A combination of the use of atropin and the induction of anti-anaphylaxis by dividing the dose of arsphenamin is more effective than either method alone.

8. A combination of the two methods may make possible the continuance of arsphenamin treatment in patients in whom repeated severe reaction would otherwise force its abandonment.

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OBSERVATIONS ON THE COMPARATIVE VALUE OF ROUTINE INTRAVENOUS TREATMENT, SPINAL DRAINAGE, AND ARSPHENAMINIZED SERUM INTRASPINALLY (SWIFT-ELLIS) IN NEUROSYPHILIS*

JOHN H. STOKES AND EARL D. OSBORNE

The treatment of neurosyphilis by the drainage of spinal fluid, in conjunction with other modes of treatment, has been brought into prominence during the last four years. Gilpin and Earley, in 1916, were the first observers to advocate this form of therapy. They reported encouraging results in three patients on Dercum's service. Following this report, Pillsbury, in 1917, reported his results with the employment of mercurial inunctions with spinal drainage. He said, "On the whole, the results are not striking and similar effects might reasonably be expected without spinal drainage." Recently, in March, 1920, Dercum has strongly advocated spinal drainage, especially in paresis and tabes. He presents the case for spinal drainage with simultaneous intravenous arspHENAMIN and routine mercurial therapy. He contends that the results obtained by the methods in which arspHENAMINIZED or mercurialized serum are employed are due not to what is introduced into the dural canal, but to the withdrawal of fluid which he asserts is always practised in connection with such methods. He believes that the results of so-called intraspinal therapy can be duplicated merely by drainage of fluid following intravenous injection. Without entering into anything suggesting argument in rebuttal, we can only state that therapists of our acquaintance who are getting good results make a practice of introducing as much or more serum than the amount of fluid withdrawn, so that reduced hydrostatic pressure as a means of causing transfer of remedial agents from the blood to the fluid can hardly be said to apply. The suggestion of Dercum that the substances introduced into the canal in intraspinal therapy

* From the Mayo Clinic and The Mayo Foundation. Reprinted from the *Journal of the American Medical Association*, 1921, lxxvi, 708-710.

are dissipated so quickly that they can produce no effect, would seem to be the opposite of the conclusions of Becht in a series of elaborate physiologic studies on the fluid in which it was found that epinephrin and nicotin are not absorbed sufficiently rapidly from the spinal canal to produce the characteristic physiologic effect on the blood pressure, and that epinephrin can be detected in the canal at least five hours after its injection. Mehrtens and MacArthur found that the penetration of arsenic through the meninges into the fluid occurs in approximately 43 per cent of cases after ordinary intravenous injection, but that this proportion increases to 92 per cent when the intravenous injection of arsphenamin is given six hours after therapeutic irritation of the patient's meninges by an intraspinal injection of his own serum. Moreover, the concentration of arsenic is three times as great for patients having preliminary serum injection as in the controls. Mehrtens and MacArthur found, moreover, that spinal drainage did not increase the percentage of arsenic penetrations of the meninges. These various observations seem to be in direct opposition to the contentions on which Dercum bases his advocacy of simple drainage.

During 1918, about fifty patients with neurosyphilis were placed on spinal drainage therapy with a view of ascertaining, if possible, the advantages of this type of medication. Our method consisted of the weekly withdrawal of from 30 to 70 c.c. of spinal fluid fifteen minutes to one hour following an intravenous injection of arsphenamin. Mercury, in the form of inunctions or the intramuscular injection of a soluble salt, was also employed in every case. Only twenty-five of the fifty patients have received sufficient treatment to be included in this review. The others either disappeared from observation or further treatment was precluded by some definite contraindication. The average number of spinal drainages in each case was five, the highest number being nine and the lowest three. On the completion of drainage the patients were placed on interim inunction treatment and reexamined after intervals of from two to nine months. The somewhat disappointing results led to their being placed on Swift-Ellis-Ogilvie intraspinal treatment. In order to extend the comparison to include an estimate of the relative effectiveness of routine intravenous treatment and of spinal drainage, the twenty-five cases with spinal drainage were subsequently compared with fifty without spinal drainage. It is difficult in work of this type, which involves all the unforeseen variations of the individual case, each with its own strain of infecting organism

and predisposed soil, to make comparisons that may be fully controlled and above criticism. For this reason we cannot offer final conclusions, but merely state that on the impressions created by this study we have ceased to place any great reliance on spinal drainage.

Response of the spinal fluid Wassermann to spinal drainage.—Of the twenty-five patients treated by routine measures with drainage, twenty-one had a positive Wassermann reaction on the spinal fluid on 0.3 and 0.4 c.c. (0.6 and 0.8 using one-fourth volume) before treatment was begun (Tables 1 and 2). Following a course of spinal drainage nine-

TABLE 1
PATIENTS RECEIVING ARSPHENAMIN INTRAVENOUSLY FOLLOWED BY SPINAL DRAINAGE

Case.	Diagnosis.	Spinal fluid before drainage.			Drain-ages.	Spinal fluid at completion of course of spinal drainage.		
		Wassermann reaction.	Nonne reaction.	Lymphocytes.		Wassermann reaction.	Nonne reaction.	Lymphocytes.
A180703	Neurosyphilis—Tabes dorsalis.....	+++	+	48	5	+++	—	3
A241147	Neurosyphilis—Tabes dorsalis.....	—	+	64	4	—	+	33
A242098	Neurosyphilis—Tabes dorsalis.....	+++	+	23	6	+++	—	20
A206279	Neurosyphilis—Juvenile paresis.....	+++	+	23	6	+++	+	13
A176751	Neurosyphilis—Early tabes dorsalis.....	+++	+	16	3	+++	+	17
A242133	Neurosyphilis—Taboparesis.....	+++	+	59	6	+++	+	R. B. C.
A236507	Neurosyphilis—General paresis.....	+++	+	15	9	+++	+	12
A237532	Neurosyphilis—Early taboparesis.....	+++	+	159	5	+++	+	22
A244843	Neurosyphilis—Tabes dorsalis.....	—	+	87	3	—	+	30
A227033	Neurosyphilis—Taboparesis.....	+++	+	71	5	+++	+	36
A217826	Neurosyphilis—Tabes dorsalis.....	+++	—	112	5	+++	—	6
A249310	Neurosyphilis—Questionable general paresis.....	+++	+	45	6	+++	+	12
A106132	Neurosyphilis—Tabes dorsalis.....	+++	+	31	4	+++	+	12
A210990	Neurosyphilis—Tabes dorsalis.....	—	—	1	4	—	—	3
A241013	Neurosyphilis—Meningeal involvement	+++	+	285	8	+++	+	36

teen, or all but two of these twenty-one patients still had positive Wassermann reactions on the spinal fluid and one of the two who became negative reverted to positive with a marked rise in cell count after a rest interval on inunctions. Of the four originally Wassermann-negative cases, all were still negative at the conclusion of treatment. It would seem that to the extent that it was applied the procedure had little effect on the Wassermann reaction on the spinal fluid.

Response of the cell count to spinal drainage.—The cell count, contrasted with the Wassermann reaction on the fluid, responded very well to drainage. The average count was 61 lymphocytes before treatment and 19 lymphocytes at the conclusion of treatment. Something suggesting a Herxheimer-like rise followed by a fall in the curve of

TABLE 2
PATIENTS RECEIVING SPINAL DRAINAGE FOLLOWED BY INTRASPINAL TREATMENT (SWIFT-ELLIS-OGLIVIE)

Cases.	Diagnosis.	Spinal fluid before drainage.			Spinal fluid at completion of course of spinal drainage.			Interval, months.	Spinal fluid on return.			Spinal fluid at completion of course of intraspinal treatment.			Lymphocytes.
		Wasser-mann reaction.	Nonne reaction.	Lymphocytes.	Wasser-mann reaction.	Nonne reaction.	Lymphocytes.		Wasser-mann reaction.	Nonne reaction.	Lymphocytes.	Wasser-mann reaction.	Nonne reaction.	Lymphocytes.	
A210102	Neurosyphilis—Taboparesis.	+++	+	131	+++	+	9	7	—	—	74	—	—	—	5
A246689	Neurosyphilis—Tabes dorsalis.	+++	+	27	—	+	40	6	+	+	8	+	+	+	10
A233423	Neurosyphilis—Tabes dorsalis.	+	+	55	+	+	19	6	+	+	109	+	+	+	5
A237653	Neurosyphilis—Chronic anterior poliomyelitis.	+	+	34	+	+	1	2	+	+	14	+	+	+	5
A342004	Neurosyphilis—Tabes dorsalis.	+++	+	90	+	+	7	3	+	+	28	+	+	+	64
A118811	Neurosyphilis—Meningeal involvement.	+++	—	13	+	+	8	9	+	+	45	+	+	+	6
A219435	Neurosyphilis—Tabes dorsalis.	+++	+	34	+	+	72	9	+	+	38	+	+	+	11
A231016	Neurosyphilis—Early tabes dorsalis, neuroretinitis.	+++	+	4	+	+	40	6	+	+	29	+	+	+	3
A260093	Neurosyphilis—Tabes dorsalis.	+++	+	27	+	+	7	6	+	+	91	+	+	+	4
A203504	Neurosyphilis—Taboparesis.	+++	+	72	+	+	7	7	+	+	—	+	+	+	—

TABLE 3

SUCCESSIVE CELL COUNTS IN CASES SHOWING HERXHEIMER-LIKE CURVES

Cases.	Lymphocytes.						
	Before Drainage.	First drainage.	Second drainage.	Third drainage.	Fourth drainage.	Fifth drainage.	Sixth drainage
A231016	4	67	157	82	20	66	72
A266094	27	43	R. B. C.	47	25	20	29
A292098	R. B. C.	23	47	R. B. C.	143	74	20
A203504	28	64	45	13	7		
A244843	87	149	49	30			
A223423	44	55	137	57	33	18	20

pleocytosis was observed in six of our twenty-five cases (Table 3 and Fig. 220). We are inclined to believe that such a rise followed by a fall in the curve of pleocytosis may occur in patients receiving routine therapy for neurosyphilis without the use of spinal drainage, inasmuch

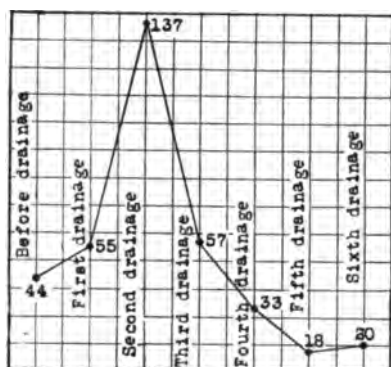


FIG. 220.—Lymphocytes in case showing Herxheimer-like curve.

as we have observed even in favorably progressing cases that the cell count in a fluid taken with the sixth intravenous arsphenamin injection may be higher than that taken five weeks before with the second injection. The completeness of the curves here presented simply pictures accurately as a result of frequent examination what we are inclined to believe may take place without spinal drainage. The interpretation of this pleocytosis as a sign of transient meningeal reaction

was borne out by the development in the patients of suggestive symptoms such as headache, dizziness, and nausea during the rise, and their subsidence during the fall of the cell count.

We have observed symptomatic Herxheimer reactions in many cases in which observations of the spinal fluid were not conducted with sufficient frequency to plot a curve of the type here presented. The reaction evidently consumes some time. It is worth while, therefore, to recall that the finding of a higher cell count on a second observation some weeks after the first is not necessarily evidence of unfavorable

progress, but may, on the other hand, be a sign of therapeutic reaction at least theoretically encouraging.

Our observation so far as the changes in the cell count with the patient under treatment are concerned is essentially confirmatory of the recently published work of Solomon and Klauder on a provocative reaction in the spinal fluid.

Study of ten patients with neurosyphilis treated by spinal drainage and subsequently by intraspinal therapy.—Following the none too striking outcome of spinal drainage ten of the twenty-five patients who had been drained were placed on the Swift-Ellis-Ogilvie arsphenaminized serum treatment from two to nine months after completing their course of spinal drainage. While it may be argued that the previous treatment prepared the patient to some extent for the intraspinal therapy, it has been our experience that the effect of single courses followed by long rest intervals is less cumulative than is often believed, and that comparison of the effect of subsequent treatment with earlier treatment is possible. On the other hand, in fairness to spinal drainage it must be recalled that it preceded intraspinal therapy, so that some of the effect of the Swift-Ellis treatment may be attributed to the cumulative effect of previous therapy in general. On the other hand, spinal drainage had been preceded by routine therapy in fourteen of the twenty-five cases, and in seven in which both spinal drainage and Swift-Ellis treatment had been instituted. The amount of treatment received prior to drainage varied from six to twenty-four arsphenamin injections (average nine injections) and fifty-four inunctions or twenty-one succinimid injections for each patient. It is evident, therefore, that the good effect of the intraspinal therapy could scarcely be regarded as merely cumulative action on relatively untreated cases. The ineffectiveness of the drainage is, of course, made the more apparent. Table 2 gives a summary of this group. Before spinal drainage was begun the spinal fluid was strongly positive in each case. In only one (Case A223423) was the Wassermann test negative, and in this case there were 55 lymphocytes. Following the course of spinal drainage two of these nine cases (Cases A248639 and A231016) showed a reversal of their Wassermann reactions to negative with a fall in cell count to within normal limits. The case originally Wassermann-negative (Case A223423) remained so and the cell count dropped to 20. Seven originally Wassermann-positive cases remained so after spinal drainage with a varying amount of improvement in the cell counts. The three pa-

tients whose spinal fluid Wassermann reactions had become negative following spinal drainage returned for observation after two had rested six months and one had rested nine months. Two of the three (Cases A223423 and A231016) showed a complete relapse to a strongly positive Wassermann reaction in the fluid, with cell counts that had relapsed to 109 and 43 respectively. The other patient remained entirely negative, with a cell count of 2. All ten patients were then placed on the Swift-Ellis-Ogilvie form of intraspinal therapy. The average number of intraspinal injections given was approximately five, the same as the number of spinal drainages. Nine of the patients still had strongly positive fluid Wassermann reactions and marked pleocytosis when intraspinal treatment was begun.

At the completion of five intraspinal treatments five patients showed a complete reversal of the spinal fluid Wassermann reaction to negative as compared with two after drainage, with a marked fall in cell count to 11 or below. In Table 2 the marked difference in response of the same patients to the two methods of treatment is more apparent. Three of the five patients are still under observation and have not relapsed.

Comparison of spinal drainage with routine intravenous therapy.—A comparative study was now undertaken of fifty cases chosen at random from our files in which only arsphenamin intravenously and mercury in the form of inunctions or the intramuscular injection of a soluble salt were administered. In other words, the cases paralleled the spinal drainage cases without the spinal drainage. The same number of arsphenamin injections and approximately the same amount of mercury were given each patient in this group as were given to patients who received drainage. The average cell count in these cases before treatment was 73, as compared with 61 in the drainage cases; at the conclusion of treatment the count was 20 and 19 cells respectively. In other words, the response of the cell count to treatment was as good in the cases routinely treated as in the drainage cases. Of the fifty patients without spinal drainage, thirty-four gave Wassermann-positive reactions on the spinal fluid before treatment. Ten of these thirty-four (29.4 per cent) were Wassermann negative at the completion of their course. On the other hand, the spinal fluid Wassermann reaction was reversed in only two (9.5 per cent) of twenty-one patients with spinal drainage. It seems probable, therefore, that routine standard treatment alone is as effective as routine treatment plus spinal drainage.

The discrepancy in favor of routine methods without drainage may perhaps be due to an unconscious selection of somewhat more refractory cases for the treatment by drainage.

CONCLUSIONS

Without making any pretense at setting forth final conclusions in the matter, in view of the difficulty of establishing adequate controls in a clinical investigation of this type, we may state that in our experience:

1. A comparison of the findings on patients receiving spinal drainage in conjunction with arsphenamin intravenously and routine mercurialization and the findings on patients receiving an equal amount of routine treatment without spinal drainage, demonstrates no superiority in favor of the drainage method.

2. The most immediate change produced by either of these methods of treatment is in the cell count.

3. A transient but marked rise followed by a fall toward normal limits occurred in patients receiving spinal drainage, and we have reason to believe that a similar Herxheimer-like curve of pleocytosis accompanied by transient exacerbation of symptoms occurs in many patients under treatment for neurosyphilis by routine methods.

4. Temporary rise in the cell count early in the course of treatment should not, therefore, necessarily be regarded as of unfavorable prognostic significance.

5. In ten patients in whom spinal drainage had produced indifferent results the administration of arsphenaminized serum intraspinally some months later produced what appeared to be more satisfactory and more permanent results.

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IS LUPUS ERYTHEMATOSUS DISCOIDES CHRONICUS DUE TO TUBERCULOSIS?*

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The question of the relationship of lupus erythematosus to tuberculosis has interested dermatologists since the time of Cazenave, who gave the disease its present name, and considered it probably identical with lupus vulgaris. Very early most French observers, on the strength of their clinical observations, maintained that lupus erythematosus was of tuberculous origin, a paratuberculosis. Dermatologists of the English, Austrian, and German schools, on the other hand, insisted that evidence favoring such a view was insufficient. Since then opinions have varied. Recently certain American authorities¹⁸ have expressed doubt as to the specific tuberculous origin of this dermatosis, and seem to favor multiple etiologic factors. Their conception, evidently based on a varied clinical experience, is in accord with my own. To verify my clinical impression I made this statistical study, approaching the question by four avenues:

1. The percentage of clinical tuberculosis detected in patients with lupus erythematosus discoides chronicus, who had been adequately studied for tuberculosis, was estimated.

2. The records were searched for patients with dermatoses ordinarily not associated with tuberculosis in order to determine, for comparative purposes, the frequency of clinical tuberculosis in these dermatoses. No record was used which did not show evidence of an adequate examination for tuberculosis.

3. The frequency of clinical tuberculosis in such dermatoses as erythema multiforme and erythema nodosum, probably in certain cases of tuberculous origin, was compared with the incidence of tuberculosis in lupus erythematosus discoides chronicus.

4. The incidence of tuberculosis shown by the records of patients with tuberculids, who had been adequately examined for tuberculosis, was compared with the frequency of tuberculosis in patients with

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lupus erythematosus discoides chronicus. It should be stated here that "patients adequately examined for tuberculosis" means patients who had been subjected to special examination for the detection of the disease in the medical sections and not merely to routine physical examination.

CLINICAL TUBERCULOSIS IN PATIENTS WITH LUPUS ERYTHEMATOUS DISCOIDES CHRONICUS

Fifty-six patients in a group of 150 with *lupus erythematosus discoides chronicus* had been specially examined for tuberculosis. The records of the others were unsatisfactory for the purpose, either because the diagnosis of *lupus erythematosus discoides chronicus* had not been definitely made, or the physical examination for tuberculosis was not adequate. Twenty (35.7 per cent) of the fifty-six patients had tuberculosis, eight (40 per cent) had glandular involvement alone, and five (25 per cent) had both glandular and other forms of tuberculosis. Seven patients (35 per cent) showed signs of tuberculosis other than glandular. Four of these were reported as probably cured. It should be observed that 65 per cent of the tuberculous lesions found in these patients were of the glandular type. Incidentally, it was noted in our group that the average age of the patient at the onset of *lupus erythematosus discoides chronicus* was thirty-three years. The youngest patient was seven years when the disease began and the oldest fifty-nine years. These facts evidently do not constitute evidence for or against tuberculosis as an etiologic agent. Realizing the various difficulties that beset the examiner in obtaining a reliable family history of tuberculosis from the average layman, I do not wish to emphasize the significance of any data obtained from the histories alone; it may be stated that our records gave a positive family history of tuberculosis in fifteen instances (27 per cent) only. Four of these were in patients with definite tuberculous infection at the time of examination.

FREQUENCY OF CLINICAL TUBERCULOSIS IN VARIOUS DERMATOSES

To find the frequency of clinically recognizable tuberculosis in dermatoses admittedly not of tuberculous origin fifty-six records of patients with miscellaneous nontuberculous dermatoses, in whom an adequate examination for tuberculosis had been made, were taken at random from 252 successive histories searched to yield the required

number. The only basis for selection was a special examination for tuberculosis. Included in the 252 cases were thirty-three cases of dermatitis herpetiformis, thirty-six of lichen planus, 145 of eczematoid dermatitis, and thirty-eight of psoriasis. The total number of histories examined, the number of patients adequately examined for tuberculosis, and the proportion of positive findings of tuberculosis are tabulated:

INCIDENCE OF TUBERCULOSIS IN MISCELLANEOUS DERMATOSES

Type of dermatosis.	Patients.	Patients adequately examined.	Tuberculosis present.
Dermatitis herpetiformis	33	7	2 (28.5 per cent)
Lichen planus	36	9	1 (11.1 per cent)
Eczematoid dermatitis	145	29	11 (38.0 per cent)
Psoriasis	38	11	4 (36.4 per cent)
Total	252	56	18 (32.1 per cent)

The tabulation shows that the percentage of clinical tuberculosis in miscellaneous dermatoses is almost as high as the incidence of tuberculosis in lupus erythematosus discoides chronicus (32.1 per cent compared with 35.7 per cent). It should be noted, however, that there was only one case with glandular tuberculosis in this group.

FREQUENCY OF CLINICAL TUBERCULOSIS IN ERYTHEMA MULTIFORME AND ERYTHEMA NODOSUM

The incidence of tuberculosis in such dermatoses as erythema multiforme and erythema nodosum was next considered. This examination is of unusual interest because erythema multiforme and erythema nodosum are probably etiologically as closely allied to lupus erythematosus discoides chronicus as any dermatosis, in the sense that their cause is undetermined, but that much evidence points to a tuberculous factor in their etiology¹¹ in some instances, and their nontuberculous²⁷ nature in others. The belief is gaining ground that other influences, for example, focal infections, may uncover the tuberculous lesion, so to speak, much as measles is known to uncover it and permit a lighting up of a lesion otherwise quiescent.³¹ Fifty-three patients with erythema multiforme and erythema nodosum in a group of ninety-six had been adequately examined for tuberculosis. Of these, seventeen (32 per

cent) had evidence of tuberculosis. Two facts are evident. The incidence of clinical tuberculosis in these dermatoses is slightly less (32 per cent) than that in such admittedly nontuberculous dermatoses as those classified under the term eczematoïd dermatitis (37.9 per cent). Neither does the percentage exceed that in all the nontuberculous dermatoses considered (32.1 per cent). It also compares favorably with the incidence of tuberculosis in lupus erythematosus discoïdes chronicus (35.7 per cent). These figures, while too small to be conclusive, suggest that erythema multiforme and erythema nodosum, like lupus erythematosus discoïdes chronicus, may both at times be of tuberculous etiology, but they may both at times be of nontuberculous etiology.

INCIDENCE OF CLINICAL TUBERCULOSIS IN THE TUBERCULIDS COMPARED
WITH ITS INCIDENCE IN LUPUS ERYTHEMATOSUS
DISCOIDES CHRONICUS

The most striking feature of this study was the contrast afforded by the incidence of clinical tuberculosis in the tuberculids when compared with its incidence in lupus erythematosus discoïdes chronicus. Thirty-seven cases of lichen scrofulosorum, erythema induratum, papulonecrotic tuberculids, folliclis, and acnitis (Barthélemy) had been adequately examined for tuberculosis. Of these, thirty-one (84 per cent) presented definite clinical evidence of infection compared with 35.7 per cent in lupus erythematosus discoïdes chronicus. The tuberculosis in eighteen (48.6 per cent) was of the glandular type only, and in four (10.8 per cent) both of glandular and some other type. Six of the patients who presented negative findings had erythema induratum. The diagnosis of one of the six is still to be regarded as doubtful after prolonged observation. In none of the foregoing cases did we find an authentic instance of the simultaneous occurrence of lupus erythematosus discoïdes chronicus and tuberculids.*

The unimportant part played by tuberculosis in lupus erythematosus discoïdes chronicus as compared with acknowledged tuberculids is so striking that one is tempted to say flatly that lupus erythematosus discoïdes chronicus cannot have the pathogenesis of a tuberculid in the accepted sense of the term.

* Among the earlier records of the department I subsequently found one instance of such association, and such an association has been reported by MacLeod,²⁸ Wile,²⁴ and others.

TUBERCULOSIS AS AN ETIOLOGIC AGENT

A review of the literature illustrates the difficulty of adding anything new to the evidence incriminating tuberculosis as an etiologic agent in lupus erythematosus discoides chronicus. It does not seem necessary to review here in detail the various arguments based on clinical observation. This has been done most thoroughly by Friedlander,¹⁴ Freshwater, Bloch and Fuchs, Wise, and others. Most of the arguments are based on evidence aiming to prove the tuberculous nature of lupus erythematosus discoides chronicus by its frequent association with other evidence of tuberculosis. The double-edged character of such arguments becomes apparent when such observers as Gunsett and Weiss and Singer come to the conclusion that tuberculosis is not a factor in the production of lupus erythematosus discoides chronicus, on diametrically contrary observations. Gunsett collected from the literature twenty cases of lupus erythematosus in which careful postmortem examinations had been made. In only nine of these was any evidence of tuberculosis found. Ten of the postmortem examinations were made under the direction of Rokitansky, and in seven instances no evidence of tuberculosis was discovered. Gunsett is well aware of the frequency of tuberculosis in general, and justly lays special emphasis on the frequent impossibility of demonstrating on postmortem examination the presence of tuberculosis in lupus erythematosus discoides chronicus. In the light of our present knowledge it certainly seems that a carefully conducted postmortem examination is worth vastly more than all the combined clinical statistics endeavoring to show the coincidence of tuberculosis and lupus erythematosus discoides chronicus.

To Weiss and Singer the association of tuberculosis with lupus erythematosus discoides chronicus means chiefly the ubiquity of tuberculosis, and is not evidence of any etiologic relationship. They found indubitable evidence of tuberculosis past or present in ten of their twelve patients, and they believe that the other two were also tuberculous. They emphasize the fact that investigators have found increasingly higher percentages of tuberculosis in their postmortem examinations, and they cite Opie as being able to demonstrate tuberculous lesions in every one of fifty patients who died of nontuberculous diseases. This pathologist used a most ingenious method of postmortem investigation. Roentgen-ray pictures were taken of the inflated and extirpated lung, followed by minute section and search with the skiagram as

a guide. These observations suggest that tuberculosis is almost universal. Since lupus erythematosus discoides chronicus is a comparatively rare disease, these observations certainly suggest that factors of moment other than tuberculosis must enter into the etiology of the disease. The results of the present study support Weiss and Singer's view not only because in nontuberculous dermatoses approximately as high an incidence of clinical tuberculosis as in lupus erythematosus discoides chronicus was apparent, but also because in lesions of the skin admittedly tuberculous, such as the tuberculids, the incidence of clinical tuberculosis is far higher. Weiss and Singer's tabulations of lupus erythematosus discoides chronicus cases correspond very closely with my data. They found a total of 225 cases, in sixty-four of which the presence or absence of tuberculosis was noted. Of these sixty-four cases, eighteen (28 per cent) showed evidence of tuberculosis and forty-six (72 per cent) did not. Our combined observations seem to indicate that clinically recognizable tuberculosis is a factor in only a moderate percentage of cases of lupus erythematosus discoides chronicus. While clinical observation thus critically examined seems to give little encouragement to a belief in the tuberculous etiology of lupus erythematosus discoides chronicus, experimental investigation at times seem all but to have proved its tuberculous origin. When the results of these investigations are critically reviewed, however, the case for a purely tuberculous etiology does not seem nearly so strong.

Tuberculosis demonstrated by tuberculin test.—It is, of course, not surprising that in cases of lupus erythematosus discoides chronicus, as in other diseases suspected of a tuberculous etiology, the tuberculin test should have been freely employed. It is at once apparent that only the focal reaction in the lupus erythematosus discoides chronicus lesion could possibly be of any significance. The von Pirquet, the intradermal, and the general reactions are only of interest so far as they signify tuberculous infection past or present. But as in a certain number of patients with lupus erythematosus discoides chronicus the systemic tuberculous infection is easily demonstrated clinically, and as tuberculosis is probably present in the majority of the remainder, as modern investigation tends to show, the tuberculin reaction is of little value. Fishberg found that between 40 and 60 per cent of humanity react to the tuberculin test. Franz was able to obtain from 60 to 70 per cent positive tuberculin reactions in several Austrian regiments. It must be remembered that he was dealing with healthy men

selected because of exceptional physical fitness. Deycke states that in European countries it is only the exceptional adult who does not react to tuberculin. It would hardly seem that the systemic tuberculin reaction can be adduced as an argument to prove the tuberculous etiology of lupus erythematosus discoides chronicus.

The focal or local reaction in the lupus erythematosus discoides chronicus lesion has been looked on as favoring the tuberculous origin of lupus erythematosus, and such a phenomenon has been reported by some good observers. Engman and McGarry have repeatedly observed this reaction, however, on the injection of dead typhoid bacilli used as a foreign protein. Barber has observed a severe focal reaction following the injection of an autogenous vaccine prepared from a tonsillar swab which gave a pure growth of long-chain streptococci. Moreover, true cutaneous tuberculosis (lupus vulgaris) is known to give focal reactions to nonspecific agents such as arsphenamin.¹⁹ It seems, therefore, that the focal phenomenon can be produced readily by other agents.

The fact that lupus erythematosus improves under the administration of tuberculin cannot be regarded as a valid argument for its tuberculous nature. Engman, Barber, and Adamson have seen patients definitely improve under the administration of other forms of internal medication. We have observed the disappearance of lupus erythematosus under a species of autogenous vaccination produced by an attack of erysipelas.³²

Demonstration of Bacillus tuberculosis by Ziehl's and Much's methods.—The demonstration of the tuberculosis bacillus directly by Ziehl's method in the sections from patches of lupus erythematosus has been frequently tried, but never successfully accomplished. When the difficulty of demonstrating the bacillus by this method from the lesions of a known tuberculous nature, such as lupus vulgaris, is considered, it is not surprising that lupus erythematosus yields negative results. In recent years Much's method has enabled observers apparently to demonstrate tuberculosis bacilli when it was impossible to find them by Ziehl's stain. The presence of Much's granules are not generally accepted, however, as proof of the tuberculous nature of any lesion. Their identity with tuberculosis bacilli is not universally accepted, and it is an acknowledged fact that it is often very difficult to distinguish between Much's granules and artefacts in sections or smears.⁷ Positive demonstrations of tuberculosis bacilli are reported in only a few instances. The organisms were all found in excised pieces of tissue from

lupus erythematosus treated by the antiformin method. Such cases have been reported by Arndt, Hidaka, Spiethoff, and Friedlander. These observers demonstrated the bacilli by both Ziehl's and Much's methods. Hidaka and Friedlander, however, are very skeptical of their significance. The former does not consider Much's granules as proof of tuberculosis. He believes that tuberculosis bacilli may easily circulate in the blood of tuberculous persons, or that they may be simulated by acid-fast bacilli found in the water supply and accidentally introduced during the experiment. These positive findings certainly need further confirmation before they can be accepted as having any significance. It should be said also that Arndt's cases were not of the chronic type. Granted that his observations were correct for the type of case he examined, it would not be proof that the chronic type did not involve some special factors of etiologic moment.

Tuberculosis proved by animal experimentation.—Undoubtedly, the experiments of greatest significance are those in which positive animal inoculations have been obtained. A positive result is probably the most dependable proof obtainable, although errors may readily be committed here also. I was able to find in the literature records of only seven positive animal experiments, and these merit most careful scrutiny.

Gougerot reported the first successful attempt at animal inoculation. His first patient had a typical lupus erythematosus of the scalp without other evidence of tuberculosis. The patch was excised and transplanted into two guinea pigs. Five months after inoculation one animal did not reveal evidence of tuberculosis on section; the other had two sclerotic matted glands with caseated centers at the site of the graft. In the caseous material a few tuberculosis bacilli were found. The liver and spleen also revealed a few small nodules with typical tuberculous structure. This case is probably the nearest approach to an experimental demonstration reported in the literature. It was evidently a typical case of lupus erythematosus discoides chronicus in a patient without other evidence of tuberculosis. The experimental evidence produced from cases with acute disseminate lupus erythematosus or from cases of an atypical type cannot be accepted as demonstrating a tuberculous etiology for lupus erythematosus discoides chronicus.

The second case reported by Gougerot is a freak or atypical lupus erythematosus. The case does not apparently belong even in the usually recognized subclasses of lupus erythematosus, but perhaps may

be regarded as an example of a vesico-ulcerative type. When authorities hold widely divergent opinions relative to the etiology and nosology of such conditions as the various types of sarcoids, nodular tuberculosis of the hypoderm, granuloma annulare, erythema elevatum diutinum and allied dermatoses, certainly no atypical cases of lupus erythematosus which may at times resemble any of these dermatoses should be used to prove the etiology of lupus erythematosus discoides chronicus. We must therefore conclude that Gougerot's second case cannot be accepted as an authentic lupus erythematosus discoides chronicus.

Ehrmann and Reines reported a case of successful animal inoculation. In their patient the lupus erythematosus discoides chronicus was, however, associated with typical papulonecrotic tuberculids on the buttocks and large tuberculous glands of the neck. The significance of a positive animal inoculation from such a case remains open to discussion. The criticism of the experiment revolves largely around the presence of active tuberculous lesions in the body. In this particular instance the presence of a tuberculid speaks for hematogenous distribution of tuberculosis bacilli. The hematogenous distribution of tuberculosis bacilli may at least be regarded as fairly well supported, for example, by the observations of Liebermeister, who believed himself able to demonstrate the tuberculosis bacilli in the blood of living patients. He not only found them in advanced stages or when the patient was moribund but also in a number of clinically mild cases. On the basis of his experimental and pathologic observations he concludes that tuberculosis bacilli are in every case periodically projected into the blood and that they may circulate in the blood without producing a miliary tuberculosis or typical metastasis. It is an accepted fact that tuberculosis of the kidney, in the vast majority of instances, is of hematogenous origin. O'Neil says, "There is ample evidence to show that the bacilli are carried to the kidney by the arterial blood in a great majority of cases. Blood infections in tuberculous patients are not uncommon, and it is a well-established fact that even with a small tuberculous focus in an active state, such as an apical lesion, there may be a temporary bacillemia during which time the bacilli may be recovered from the blood. Further evidence that tubercle bacilli reach the kidney more or less constantly is shown by numerous observations that in pulmonary tuberculosis a filtration of bacteria may take place through the kidneys which after death show no evidence of tuberculous disease." Presence of tuberculosis bacilli

in the circulating blood should warn us not to lay too much stress on the presence of these bacilli in excised pieces of tissue. The demonstrated bacilli could in certain instances have been present in the capillaries of the lesion. This presence of bacilli in the capillaries could easily occur in early lesions of lupus erythematosus discoides chronicus with their marked vascular dilatation and blood stasis.

Probably no experimental work on the tuberculous nature of lupus erythematosus discoides chronicus has been more carefully controlled than that of Bloch and Fuchs. These authors review carefully all the evidence brought forward for or against the tuberculous etiology of the condition. They conclude that unless it is the results of positive animal inoculation, none of the evidence brought forward in behalf of tuberculous etiology is so strong that other evidence equally valid cannot be found to offset it. Believing that positive animal inoculations would be the only conclusive proof, these observers made determined efforts to produce tuberculosis in guinea pigs by inoculating them with pieces of the tissue from lupus erythematosus. They were able to demonstrate tuberculosis bacilli in four cases. In two instances in the first series of animals the inoculation was successful, once in the second series, and once not until in the third series. The authors believe that their success was due to repeated animal passage; the gradually increasing virulency of the bacillus finally produced tuberculous lesions in the experimental animal. Here again the value of the experiments is impaired by the fact that three of the patients had active tuberculosis. One of the patients had an active disseminate lupus erythematosus which closely resembled the type first described by Kaposi as *erysipelas faciei perstans*. This case must be eliminated because of the doubtful nosologic classification of the dermatosis. The fourth case, while not clinically tuberculous, reacted severely to 1 mg. original tuberculin. In all of these cases the possibility that the patient's blood contained circulating tuberculosis bacilli and that, as Liebermeister suggests, these might have lodged in the capillaries, must be considered. Certainly it would seem that much better material to prove the purely tuberculous etiology of lupus erythematosus discoides chronicus could have been chosen. To prove that lupus erythematosus discoides chronicus is a true tuberculosis, typical cases of lupus erythematosus discoides chronicus without other clinical manifestations of tuberculosis should be selected. There is an abundance of such material, as the cases reported in the English and American literature and those in this series readily attest. It

may be that such experiments have been made and proved uniformly negative, and therefore have not been reported. To date the only case of positive animal inoculation that will endure a critical review is the first case reported by Gougerot. Even here accidental retention of bacilli in the morbid process is not eliminated. This case, however, is only a single instance and needs confirmation before it can be accepted at its face value.

Cutaneous allergic phenomena.—In a consideration of reactions of the skin many suggestive points bearing on a possible nonspecific character in the tuberculin reaction in lupus erythematosus discoides chronicus may be found. The allergic reaction of the skin to substances introduced intradermally is now well recognized in a number of clinical conditions. The conception of a nonspecific element in this phenomenon has received important support from the study of cutaneous allergic phenomena in late syphilis. Such apparently specific substances as Klausner's palladin and Noguchi's luetin have been shown to produce their reactions by a nonspecific mechanism. Boas and Stürup demonstrated a typical palladin reaction in late syphilis by using extracts of chancroidal bubo from a nonsyphilitic patient. Boas and Ditlevsen duplicated this experiment by producing a luetin reaction in late syphilis with gonococcal and colon bacillus suspension. Sherrick has gone a step farther and evidently artificially produced by the administration of iodids the cutaneous allergic state. He also observed that such colloidal substances as agar and starch gave similar reactions. Probably his most interesting observation was his reactivation of a practically involuted luetin reaction by subsequent administration of iodids. Stokes showed that agar makes an entirely satisfactory substitute for luetin in the luetin test applied in late syphilis, and that the reaction and the allergy on which it depends are alike nonspecific. He was also able to produce, artificially, a cutaneous allergy clinically similar to that produced in late syphilis by the injection of a homologous protein in the form of an emulsion of normal skin. By a series of injections he produced a reactivity to agar which in all respects experimentally imitated the allergy of late syphilis. These observations are essentially a proof that cutaneous allergy of certain types observed in a disease like syphilis can be imitated artificially by the introduction of proteins other than those of the specific organisms of the disease. Thus far tuberculin reactions seem usually to have been regarded as specific antigen-antibody phenomena. The similarity of

allergic phenomena in the skin in tuberculosis and in late syphilis makes the conception that the tuberculin reaction may be less specific in character than is generally supposed seem not unreasonable. Jadasohn's attempt to explain his observations on tuberculin reactions in certain syphilitic lesions by what he calls "group reactions" are not without interest in this connection. Ingenious theories have been devised to explain the failure to react to tuberculin in certain types of tuberculous subjects. The possible lack of specificity in the reagent and the absence of certain specific factors usually seem to be overlooked. It must be conceded, however, that experimental proof of the completely nonspecific character of the tuberculin reaction is apparently lacking unless that produced by Meirowsky can be accepted as such.

Whether or not we accept the allergic phenomenon as specific in character, the interesting intradermal injection experiments conducted by Bloch and Fuchs and used to support the theory that lupus erythematosus discoides chronicus is tuberculous in etiology are open to other interpretations than those the authors adopt. They injected intradermally extracts made from lupus erythematosus tissue into patients hypersensitive to tuberculin and argued from the reactivation of the papule by the subsequent injection of tuberculin that the extract contained either the bacilli or their toxins. Stokes conducted an experiment, in which the experimental conditions were similar to those of Bloch and Fuchs, to prove the nonspecific character of intradermal reactions. His patient was a late syphilitic with psoriatic lesions. Emulsion of the normal skin administered intradermally gave a definite nodular reaction. Another injection of emulsion of a psoriatic lesion not obtained from the patient's skin, given seven days later, not only formed a definite nodule, but produced a striking increase in the size of the first nodule. From the observation of this author it may be argued that in a sensitive person cutaneous allergic phenomena may be obtained with a nonspecific substance such as emulsion of the skin of a healthy person. Thus nonspecific allergic responses may be obtained perhaps from an emulsion of tissue made from a lupus erythematosus lesion when injected into a subject highly sensitive to tuberculin. Bloch and Fuchs' inference that the lupus erythematosus lesion contains either dead tuberculous bacilli or their toxins can scarcely be unqualifiedly accepted. Another weakness of the intradermal tests performed by Bloch and Fuchs is that they used not only emulsions of lupus erythematosus, but that by doing this they actually used skin

from admittedly tuberculous patients. To make their tests more significant a control should have been instituted by using for the control emulsion apparently healthy skin from the patients to learn whether the same phenomena might not have been produced as was produced by the emulsion from the lupus erythematosus lesion.

COMMENT

It is apparent, therefore, that the tuberculous origin of lupus erythematosus discoides chronicus has not been proved by any of the experimental methods reported. The most modern and comprehensive clinical studies, on the other hand, definitely favor a belief in varied etiologic factors. It seems experimental work endeavoring to prove this latter conception is more promising than attempts to prove its purely tuberculous etiology.

CONCLUSIONS

1. The incidence of clinical tuberculosis in dermatoses admittedly of nontuberculous origin (32.1 per cent) is approximately as high as in lupus erythematosus discoides chronicus (35.7 per cent).

2. Clinical tuberculosis is no more frequent in dermatoses like erythema multiforme and erythema nodosum (32 per cent), in some instances apparently of tuberculous origin, than in lupus erythematosus discoides chronicus (35.7 per cent).

3. The frequency of clinical tuberculosis in patients with known tuberculids (84 per cent) presents a striking contrast compared with the frequency of clinical tuberculosis observed in lupus erythematosus discoides chronicus (35.7 per cent). This contrast is so great that the belief seems acceptable that lupus erythematosus discoides chronicus cannot have a pathogenesis identical with that of the tuberculids.

4. The tuberculous origin of lupus erythematosus discoides chronicus has not been proved by experimental work. Clinical observation, including this statistical study, seems to favor varied etiologic factors.

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THE TREATMENT OF LATE SYPHILIS AND OF SYPHILIS IN MOTHER AND CHILD: A RÉSUMÉ OF PRINCIPLES*

JOHN H. STOKES

The problem of the treatment of late syphilis differs in essential particulars from that of early or of true asymptomatic (latent) syphilis. In early syphilis we are still, in spite of the disturbing revelations of Warthin,^{50, 51} of Brown and Pearce,^{6, 7} and of Eberson,^{11, 12} striving for radical cure of the infection. In the late stages of the disease the problem becomes one of symptomatic improvement and arrest. The early infection usually involves the unimpaired human body. In the late years of the infection the physiologic changes of advancing years are added to the disabilities produced by the action of the disease on vital structures. The characteristic reaction of the body to the syphilitic infection opposes another obstacle to treatment. The slowly progressive fibrosis walls off the organism from the carriers of remedial agents, the blood and lymph. By the induced obliterative endarteritis, the accessibility of foci to spirocheticides injected into the blood or distributed by it is probably materially reduced. In the slowly progressing or latent infection there must also exist a balance between the offensive powers of the organism and the defensive powers of the host. If the organism could be confined within the infected individual and this balance be perfectly maintained, the commensalism would serve all the purposes of the radical treatment methods of the "extirpators." The large majority of late syphilitics have probably affected some measure of compromise with the spirochetal invader, and judgment must be exercised in the disturbance of this relation.

THE APPRAISAL OF POSSIBILITIES ON THERAPEUTIC DECISIONS

The aim of treatment in late syphilis is to carry the infected individual through the fulness of his years, with maximum attainable

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efficiency and minimum danger to his contacts and to the social order. The first step in the treatment of late syphilis is an appraisal of possibilities, including:

1. An estimate of life expectancy based on age, on damage already done, on the supposed activity and rate of progress of the process, and on its probable refractoriness to treatment.
2. An estimate of the handicaps imposed by complications not directly due to syphilis, such as tuberculosis, nonsyphilitic mental disease, hypertension, chronic interstitial nephritis, diabetes, and so forth.
3. An estimate of the tolerance of the patient for the various methods of treatment available.
4. An estimate of the probable response to treatment of the most vital structures involved.

Treat late syphilis by the indications in vital structures and not in structures nonessential to life.

Only a searching examination of the entire body can provide the information for such an appraisal. While the milder forms of treatment may be begun, arsphenamin should seldom be administered until this appraisal is reasonably complete. The inherent crudity of our methods of estimating the condition of many important structures must be remembered and allowed for in making the estimates mentioned. Particularly in involvements of the vascular system is this caution important.

The Herxheimer reaction is as much a feature of late syphilis as of the acute infection. It must never be lost sight of, and the possibility that it will have serious effects, either from the location of the involved structure, as in the case of the larynx or a cerebral vessel, or from its functional importance, as in the case of the myocardium, must be carefully weighed. In general, it is conservative to give all individuals affected with late syphilis mercurial preparation.

The control of infectiousness in late syphilis, while traditionally of little import, deserves more consideration, in the light of recent work on carriers,¹² especially in the woman who is pregnant or may become pregnant, or in the potential father of children. It is, I believe, a good rule that late cases deserve nearly as much arsphenamin as early cases for the control of this aspect under the limitations imposed by the preliminary survey and the progress of the case.

Adjustments required by the process of healing are factors in thera-

peutic decisions in late syphilis. When healing begins under treatment, the attempt made by the body to compensate for a pathologic change is disturbed, made to take another direction. An adjustment to the effects of cicatricial contracture as well as to the Herxheimer reaction must be made, at times with a paradoxical increase in symptoms, as pointed out by Wile³³ for syphilitic hepatic cirrhosis. Cicatricial stenosis of the esophagus and rectum, even of the hour-glass stomach, occurs. I am inclined to believe that so far as the heart is concerned, acute myocardial ischemia, anginal attacks of increased severity, even the development of certain physical signs of aortitis and aneurysm, may be the results of too energetic treatment and too rapid healing.*

In the complete appraisal of a case consideration should be given to the vasculotoxicity of arsphenamin,† its hepatotoxicity,‡ and the seriousness of cutaneous exfoliative accidents. At first a theoretic consideration, these items have acquired a very real meaning in my experience with late syphilis. The relatively low toxicity of arsphenamin for the kidney makes it a serviceable drug in nephritis, but there is a notable exception. In low renal function from back pressure, and in pyelonephritis, often a complication of neurosyphilis, it must be used with caution. The history of previous dermatitis as a relative contraindication to arsphenamin does not receive the attention it deserves.

The renotropism of mercury, its ability by certain modes of administration to increase the cutaneous reactivity to arsphenamin, its depressant action when overdone and the unfavorable effect on severe anemias, described by Foucar and myself, are among the principal points to be considered. The old-time bugbears of stomatitis, salivation, and gastro-intestinal disturbance have been reduced to relative insignificance by dental prophylaxis, diet, and intelligence in dosage.

* I was interested to find Hubert³⁶ in accord with me on this point.

† An interesting suggestion that cardiac dilatation after arsphenamin is due to increased pulmonary pressure produced by the obstruction of the circulation or vasoconstriction, and is dependent on the alkalinity of the preparation, is made by Smith.⁴⁴ This, combined with the observation that neo-arsphenamin is not precipitated in the blood (Schamberg, Kolmer, and Raiziss⁴¹), would seem to suggest the desirability of neo-arsphenamin in cardiac syphilis.

‡ The numerous recent articles on jaundice as a complication due to the toxic action of arsphenamin are reviewed from the standpoint of a possible infectious factor in Stokes', Ruedemann's, and Lemon's paper.⁴⁷ Milian continues his vigorous defense of treatment. See also Hallam.³⁹

As in its resistance to the disease itself the body shows a generous margin of safety, notwithstanding the effect of prolonged or massive treatment, so no symptoms or good recoveries may result from the most flagrant abuse of both arsenic and mercury. But I have always felt that the avoidance rather than the correction of toxic or debilitating effects is the ideal, and to that end have insisted on a number of precautions against complications which in the end, I believe, protect patients from the small but cumulative insults which too often keep them in a substandard condition under intensive treatment, even though the individual by-effect may not become conspicuous in itself. In late syphilis, in which the margin between treatment requirements and treatment tolerance is often very small, such protective measures may make all the difference between success and failure. In the nine cardinal rules for the management of the excretory mechanism which I shall quote here from my discussion of this point before the Institute for Venereal Disease Control, I should mention that the emphasis on microscopic blood as an evidence of renal damage is drawn from an unpublished study, by Wilder and myself, of the effect of prolonged intensive treatment for syphilis on the kidney. I want also to direct attention to the influence of the atonic bladder with retention symptoms in retarding the progress of patients who would otherwise do well. I am satisfied that the terminal picture in more than one practically arrested but nonetheless fatal case of neurosyphilis is a composite of depressed renal function and ascending infection of the urinary tract.

MANAGEMENT OF THE EXCRETORY MECHANISM

1. A cathartic should be given after each arsphenamin injection, and a mild laxative during the course.
2. A weekly urine examination should be the rule.
3. Special attention should be paid to (a) casts, (b) red blood cells, and (c) pus in the urine (catheterized in women).
4. Many or persistent casts mean renal irritation. Occasional showers are not significant.
5. Red blood cells of renal origin mean renal injury.
6. Pus or blood of vesical origin may be an index of cystitis due to urinary retention. In neurosyphilitics with pyuria search should be made for atonic or "cord" bladder with residual urine, secondary cystitis and pyelonephritis, rising blood urea, and falling phenolsulphonephthalein excretion.

7. The excretory mechanism should be protected by (a) extirpation of focal infections, (b) administration of fluids and alkaline diuretics (*potus imperialis*), (c) catheterization and irrigation of neurogenous bladders, (d) diet regulation (low proteins), and (e) suspension or moderation of treatment if other measures fail.
8. The physician should not discharge a neurosyphilitic patient without being satisfied with regard to his renal function, his blood urea content, and the integrity of his bladder mechanism.
9. Every tabetic patient should be regarded as potentially uremic.

FACTORS IN A SUCCESSFUL THERAPY

Schamberg, in a personal communication, has suggested that the simultaneous administration of arsphenamin and mercury results in the retention of the arsenic with increased risk of exfoliative accidents.* That this retention is so serious as to justify abandoning the simultaneous use of the two drugs I have not as yet been able to convince myself from clinical evidence. Exfoliative accidents in my service come in waves, and have had what seemed to be more than a casual relation to intercurrent and focal infection.

The "broken immunity" of arsphenamin-treated early syphilis, long familiar in clinical experience and now experimentally verified by Brown and Pearce,⁸ has, I believe, occasional homologues in late syphilis.† All of you have no doubt seen the marked acceleration of the unfavorable progress of some cases of neurosyphilis following arsphenamin, scarcely explainable as mere arsenic fastness. I believe it is a conservative practice never to terminate a period of treatment with arsphenamin, but to finish with mercury, if it be only by mouth.

In early syphilis symptoms have little meaning as therapeutic guides; in late syphilis they may be supremely important; in fact, their disappearance may be the sole criterion of successful therapy. Eighty-five per cent of late syphilitics, in our experience, selected with only a reasonable degree of discrimination as to therapeutic outlook, should undergo symptomatic arrest and be ultimately placeable on observation.⁴⁶ One is occasionally disconcerted by the symptomatic Herxheimer flare-up which dominates the picture during the first three or four weeks of a moderately intensive course. The changes in the Wassermann reaction, while of interest, are not the sole evidence of the

* See Klauder and Kolmer.²⁷

† See Bronfenbrenner and Schlesinger¹ on the unfavorable effect of minute dosage.

efficacy of a method of treatment, and are in fact at times not even an important consideration. In general a persistent positive reaction is a signal for a rechecking of the fundamental examination and appraisal of the case, and a Wassermann relapse calls for more treatment in the absence of contraindications.

A legitimate distinction should be drawn, in estimating the progress of late syphilis under treatment, between scars and evidences of activity. It is a matter of little moment that a tabetic patient does not recover his knee jerks or a patient with cardiac disease get rid of his aortic murmur. On the other hand, it is decidedly in point if anginal attacks increase in frequency in coronary sclerosis, or if a patient with diffuse hepatitis has a recurrence of jaundice, or the liver fails to decrease in size. Paradoxical pictures at times occur, in which the signs representing scars become more conspicuous as the symptoms representing functional impairment disappear. Ascites developing in hepatic cirrhosis under treatment,⁵³ bone sequestra discharged through a sinus, atrophy of the optic nerve as a marked neuroretinitis involutes, pulsation in an aneurysm as the periaortitis subsides, are examples in point. Failure of structural improvement to occur even with marked symptomatic improvement is familiar enough in aneurysm and gastric syphilis. Functional improvement may also outstrip all expectations based on the recognized structural change, particularly in inflammatory processes. In the eye and ear gains in sight and hearing sometimes have a qualitative rather than quantitative character and may again exceed all expectations.

How far shall treatment be carried after the disappearance of symptoms when the signs are not such as to furnish a guide to the progress of the case? In general, I should say to the point of giving as much treatment as in an early case, provided tolerance permits. This is a vital proviso. The abuse of a patient's tolerance of treatment in late syphilis even more than in early syphilis is, I believe, a serious error, since it is impossible to predict that the course of his infection may not be such that he will be under treatment at intervals all his life. On the other hand, timidity in using effective measures may be precisely the thing which projects the patient on to the other horn of the dilemma. It is for these reasons that I lay much stress on the use of every available means in late syphilis to improve the general status of the patient and to protect him specifically from therapeutic by-effects. When objective guides to the effect of treatment exist, I have found it well

to persist beyond the first negative finding, so as to prevent relapse. The question as to whether relapse can be indefinitely postponed by this means remains as yet unsettled. In general I prefer mercury for the supporter of the resistance that prevents relapse, but I have seldom felt it necessary to urge the life-long "forty rubs a year" if the patient would consent to periodic complete examination. Dismissal of the patient with any such blanket directions seems to me to lay him open to all the uncertainties of an infection kept below the threshold of his own observation by self-medication.

The therapist, in late syphilis, must modify a symptomatic outlook with a preventive trend of mind. This will stimulate him to more complete examination, with a view to finding all the types of involvement in a given case.* It will lead him to regulate the life of his patient so as to put the least possible strain on his weakest points, and to conduct his treatment so that an involvement just in its beginnings may not come to the front later as some more conspicuous symptom subsides.

The therapeutic test is so much more important in late syphilis than in early infections that attention should be called to some of its pitfalls. Therapeutic tests in general have meaning only when the patient presents a definite and, as far as possible, a visible pathologic lesion, on which quantitative estimates of improvement can be made. Mere gain in weight, disappearance of indefinite pains, malaise or non-descript subjective symptoms are usually meaningless. Iodid therapeutic tests, popular with the departing generation, are untrustworthy. So are arsphenamin therapeutic tests. I have made and seen made erroneous diagnoses of gumma of the lymph nodes with partial positive Wassermann tests, I have seen tuberculous keratitis confused with syphilitic keratitis, lupus vulgaris, erythematous lupus, sarcoids, and tuberculids make striking improvement under arsphenamin. Mercury is probably more nearly immune from such nonspecific effects than either iodids or arsphenamin, although it is well to recall its action in lichen planus, and in occasional cases of sporotrichosis. Carcinoma of the stomach makes false responses to arsphenamin alone and sometimes in combination with mercury. One of the reasons a noted neurologist gave for objecting to the dermatologist as a syphilographer was his

* Studies of the multiform types of involvement often presented by patients with late syphilis seem to have been made largely by internists concerned with cardiovascular conditions. See also Stokes and Busman.*

ignorance of the false positive therapeutic test for syphilis in multiple sclerosis. Pseudo-Herxheimer reactions in tuberculous processes occasionally create a deceptive effect.*

STANDARDIZATION OF TREATMENT

Standardization and routinization of the treatment of syphilis is much easier in the early months or years of the disease than in the late. Yet I would not for a moment substitute unlimited individualization for the good effects of system and regularity in the majority of cases. But back of any systematizing of treatment must lie a willingness to think of the disease as a whole, and of the patient as a human being. I have already sufficiently emphasized, in referring to the complete examination, the need of identifying every type of involvement in a given case. The same emphasis can be transferred to therapeutic management. In explaining to patients why I wish their eyes, teeth, tonsils, stomachs, bladders, and appendixes to have attention when their trouble is syphilis of the heart or of the liver, I often use the maxim of the service chief of the best automobile repair plant I know: "Don't listen to the owner's story about this creak and that rattle, and go by that. Go through the car and put her back as nearly as possible into the shape she was in when she left the factory." Do that with late syphilis and it will not need the experimental studies of a Brown or Pearce to teach you that the course of syphilis is often as much modified by the things we leave undone as by the things we do. Bring the patient, in the course of your management of his case, as nearly up to the standard of normality for his age and sex as possible. Do, so far as possible, an overhauling and not a patching job.

In my few words concerning organized treatment I shall not even attempt an account of the endless variations proposed by different therapists. I do want to suggest, however, that we bear in mind a few principles. First, a heavy responsibility rests on the proposers of systems. Nothing is more eagerly sought after nor more frankly abused by the tyro, and even by the expert, than the rule of thumb. Yet, on the other hand, if there is any one factor which in my experience prevents the arrest or cure of syphilis, it is desultory and unsystematic management. In late syphilis, I believe, roughly speaking, in trying for radical results by combined spirillicidal and resistance-building

* The original observations on this point have been confirmed by my experience. See Herxheimer and Altmann.^{21, 22}

methods, rather than by the one or the other exclusively. Whether we obtain radical results or not, only time can decide. Life-long arrest means almost as much to the patient as extirpation. A frankly spirillicidal technic such as that of Pollitzer seems to me inapplicable to most of the cases which I am considering. I do not feel that its ability to reverse the Wassermann test, so frequently mentioned, is full and sufficient evidence of its effectiveness. It is too difficult to judge the extent and type of involvement of important structures, even with the most careful preliminary examination, to justify a system of unqualified therapeutic bludgeoning. Recent continental opinion seems to be increasingly tending toward moderation, especially in the early months of the treatment of late syphilis.* For the occasional patient with a high resistance to treatment and a threatening, though not as yet actually grave lesion, shortening of the intervals between arsphenamin injections with large doses is justifiable in endeavoring to reach an otherwise inaccessible focus. The favorable reports of users of such methods as Sicard's,† with its enormous total and minute individual dosage, and the enthusiasm of the "Pollitzerizers," with their enormous individual and relatively small total dosages, are really tributes not to any individual system, but to the wonderful variability of the disease and to that wide margin of safety for most patients, which enables almost any system that does not grossly violate the few outstanding rules of the game, to tip the delicate balance between progress and arrest, in the favorable direction. To my mind the essence of the modern treatment of syphilis is system and observation, and in the end those of the modern treatment technics which best perfect the observational aspect will show the lowest ultimate mortality.

TREATMENT OF SPECIAL TYPES

May I, in a series of idiographic sentences, lay before you some of the high points of my observations on the treatment of special types of late syphilis?

Osseous syphilis.—Arsphenamin deserves a conspicuous place for its promptness of action and the symptomatic relief which it affords in osseous syphilis.²⁵ Since the Herxheimer reaction is unimportant, ad-

* This is especially true, of course, of vascular complications. See Kothny and Müller-Deham,²⁶ who review the German literature with reference to this question.

† The French seem to have had a penchant for small dosage, as witness, Queyrat and Pinard.²⁶ Gougerot¹⁹ states that the larger doses are gaining popularity in early syphilis.

ministration may be begun at once. Arsphenamin renders iodids unnecessary, as pointed out by Jeans. Cases with delayed response and much suppuration should be searched for sequestrums by roentgen-ray and direct examination, but surgical removal should not be attempted until after some months of intensive treatment.* Progressive osseous syphilis of the nose should be searched for epithelioma, and epithelioma in the nose may simulate late syphilis very closely or be superposed on it. Mercury and arsphenamin administered together in osseous syphilis are more effective than either alone. Osteo-arthritis can be made to involute under treatment, but the Charcot joint when once fully developed does not respond. No plastic work on bone syphilis should be attempted until after at least a year of intensive treatment, with a negative Wassermann reaction. The coincidence of negative Wassermann reactions with a still active syphilis of the nasal septum is responsible for more than one fallen bridge following operative interference. Hydrarthroses, not frankly of focal or tuberculous origin, should always have a therapeutic test. There is no object in making therapeutic tests on healed osseous lesions.

Cardiovascular syphilis.—Cardiovascular involvement is probably present to some degree in nearly all late syphilis and should be searched for. The presence of obvious signs means a fairly advanced process.† The condition of the coronary arteries, difficult to predict from either examination or history, is, I believe, very important. Necropsy experience has made us realize that patients who are seemingly good symptomatic risks may have such a degree of occlusion that death results under treatment from the Herxheimer reaction, or the effects of too rapid healing.‡ Myocardial protest against arsphenamin, even in early cases, can be recognized by transient edema and a dilatation which responds to digitalis. Weeks or sometimes even months of mercurial preparation with inunctions and moderate doses of iodids are preferable to the immediate use of arsphenamin.§ If arsphenamin is used the dosage

* For the surgical management of this complication in osteitis of the skull, where it is especially obstinate, see Adson.²

† Reid's article is an excellent review of the findings in 105 cases, with a digest of the literature.²⁷ See also Babcock² and Hoover.²⁸

‡ I have been glad to find that my observations accord with those of Hubert from Romberg's Clinic.²⁸

§ The various authors mentioned and their citations from the literature show that no unanimity of opinion on this point exists as yet. The value of arsphenamin, used with caution, is generally conceded now. Hirschfelder is a notable exception.²²

should be small, and several observers have expressed a decided preference for neo-arsphenamin.* In dealing with combined neurosyphilis and cardiovascular syphilis, the cardiovascular lesion is usually the handicap and makes intraspinal treatment necessary. Aneurysms too early treated with arsphenamin may rupture and a certain amount of symptomatic advance, in the form of developing expansile pulsation,† sometimes follows too rapid resolution of the mesaortitis and mediasinitis under intensive treatment. Rest in bed affects introspective and hyperactive types unfavorably, but cannot be avoided in threatened or actual decompensation. The anxiety neurosis of these patients is often more serious and obstinate than their syphilis. The patient must be reeducated to a matter-of-fact outlook and uniform level of activity, without peaks of strain, reduced as the situation may require. At times even an assumed optimism in a consultant transforms the picture. Bromids are a valuable adjunct. Patients with cardiac disorders must be protected from gains in weight. Hypertension with an hypertrophied heart or a well-compensated valvular lesion‡ has as a rule an excellent tolerance of treatment. Heroic iodid administration in cardiovascular syphilis has no special advantages over smaller dosage that we have been able to recognize.§

Hepatic and splenic syphilis.—A liver palpable just below the costal margin following the first or second arsphenamin injection, with a slight tinging of the scleræ, is sometimes all the evidence of diffuse hepatitis recognizable in a given case. Obvious damage to the liver calls for some caution with arsphenamin. On the other hand, the *post hoc* conclusion that all jaundice following treatment for syphilis is due to the medication is unwarranted.¶ The average patient with hepatitis, diffuse or gummatous, tolerates mercury well, and is the better for from two to six weeks of inunctions and iodids, or if much debilitated, mixed treatment by mouth with rest in bed. Only in the very late cases is exhibited the therapeutic paradox⁵³ of increasing ascites with shrinkage

* See footnote*, p. 673. See also Kothny and Müller-Deham.²⁹

† Hubert²⁸ gives orthodiagraphic evidence of the enlargement of the aneurysm. Goldscheider²⁷ asserts that in small aneurysms some reduction may occur.

‡ Hirschfelder²⁵ and Reid²⁷ discuss the fall in blood pressure due to arsphenamin as a contraindication.

§ Hoppe-Seyler²⁴ advocates intravenous iodid.

¶ Syphilitic acute yellow atrophy (toxic hepatitis) is not considered here, since it is an accompaniment of early syphilis. A key to the recent French quasi-polemic writings on this subject can be obtained from Milian.²⁶ See footnote‡, p. 667.

of the liver. In my experience although transient ascites, or an increase of fluid with the Herxheimer reaction, is common, a true therapeutic paradox is rare. When it occurs, and tapping intervals grow progressively shorter, the Talma operation should be resorted to. The good results have been attested by Riesman. The prognosis of hepatic syphilis, if treatment is not pushed too hard and the patient is not moribund, is good, contrary to the usual belief.* Renal irritability is sometimes a serious matter, and demands much attention to foci of infection, diet, and so forth. Amyloid degeneration of the kidney, while a serious complication, does not flatly contraindicate fairly energetic therapy.

In marked splenomegaly the response of the fibrous spleen, in my experience, has not been very good, and when there is accompanying anemia, splenectomy performed by a competent operator yields good results.† I have an impression that more effective therapeutic tests on splenomegaly would mean more syphilis recognized and fewer splenectomies performed.¹⁰

Gastro-intestinal syphilis.—Gastric symptoms, excluding the frank crises of tabes dorsalis, are present in about one-fourth of the cases of late syphilis.‡ If the clinical picture be other than carcinoma, with a positive Wassermann reaction, therapy takes precedence over operation. This is of course especially true of hour-glass deformities. But if carcinoma is the probable diagnosis and operability prospects are good, exploration should come first and treatment second if the findings at exploration confirm the diagnosis of syphilis. Persistence of gastric symptoms in other than frank crises after the first few weeks of treatment calls for further search in which an astute clinician will often be rewarded with the finding of duodenal ulcer, appendicitis, or other pathologic conditions, slighted or lost sight of when the positive Wassermann reaction was found. Persistent morning nausea, instead of periodic attacks, has in my experience sometimes been a symptom of morphinism complicating gastric crises. In this connection I cannot refrain from protest at the readiness with which physicians at large prescribe morphin for spasmodic abdominal pain. The tradition has cost lives, for there are few problems more unmanageable than a

* Wile²² takes the opposite view; McNeil²¹ agrees with me.

† A recent complete summary of the status of splenectomy in therapeutics is that of Giffin.¹⁶

‡ This is the experience of the Mayo Clinic as summarized by Stokes and Brehmer.²³

morphin addict with crises. Arsphenamin is the drug of election in gastric syphilis. The response is one of the most gratifying in the entire field of late syphilis, and seems but rarely dependent on the extent of anatomic change as indicated by the roentgen ray, except in the case of linitis plastica.* A gain of 100 pounds in weight occurred in a patient in whom, at necropsy following influenza, a stricture 10 cm. long, near the pyloric end of the stomach, that would not pass a lead pencil was found. The starvation acidosis in these cases may need consideration. With involvement of the esophagus and of the rectum, the outlook is proportional to the ratio between active inflammatory infiltration and scar. Patients in the late stages have a poor outlook for medical relief.

Renal syphilis.—Before instituting therapeutic tests for gumma of the kidney one should be reasonably sure that one is not dealing with hypernephroma. Infected kidneys react unfavorably to arsphenamin. Other types of nephritis and nephroses tolerate it much better than mercury and it may be employed with a phenolsulphonephthalein output of zero without ill effect, provided this low function is not due to urinary retention. Therapeutic tests for syphilitic nephritis are not always infallible, even though the nephritis may respond at the outset to some extent to arsphenamin. A nephrosis, with a high albuminuria in the absence of blood and casts and with normal function, may develop late in a vigorous course of treatment.†

Anemia in syphilis.—The severe anemias which form a rare complication or accompaniment of late syphilis respond, on the whole, better to arsphenamin than to mercury, although neither is able permanently to influence the course of a pernicious type in the very large majority of cases.‡¹⁵ In fact, I have seen only one case of primary anemia in which the response led me to expect a cure. Avoidance of reactions is highly important. The occurrence of false positive Wassermann reactions in primary anemias has led to more than one disappointing therapeutic test. Anemias of secondary type of great persistence, largely uninfluenced or at most only temporarily influenced by any form of

* Sailer¹⁰ advises treatment for syphilis when linitis plastica is associated with a positive Wassermann reaction. The occurrence of structural improvement in gastric syphilis has been demonstrated by Eusterman.¹²

† Lankhout²⁰ calls attention to this nephrosis, but ascribes it to the disease and not to treatment.

‡ Gorke¹⁸ has just reported a rare aplastic anemia due to arsphenamin in hyper-susceptible persons.

treatment, occur in late syphilis. One that I recall responded to removal of a septic gallbladder.

Wassermann-resistant patients,⁴⁶ instead of being dismissed with reassurances, need, I believe, intensive study and lifelong observation. Paradoxically, however, I do not believe the reversal of the Wassermann reaction to be an end in itself, since its relation to the structural or functional integrity of any organ is as yet obscure. As one's experience with modern therapy increases fixed positive reactions become fewer, especially following the prolonged use of inunctions. The Pollitzer technic is especially extolled as a means of reversing resistant cases, but should only be used after a comprehensive survey of the case. Other conditions besides paresis may underlie an irreversible test. The reputed resistant Wassermann reaction in children has not materialized in either Jeans' experience or my own. I have seen nothing to confirm Strickler's impressions of the influence of arsphenamin in the production of false or persistent positives.*

Syphilis of the eye.—I am returning to Ehrlich's original belief that arsphenamin is distinctly contraindicated in some cases of simple primary optic atrophy (not secondary to neuroretinitis or choked disc), at least in the early months of the course. I have seen a patient with good vision go totally blind with four arsphenamin injections, and another with primary optic atrophy, due to high myopia, have to be transferred to mercury because of its action. On the other hand, focal infections in the mouth, stirred up by mercury, occasionally cause trouble from the other direction. Treatment for syphilis, especially with arsphenamin and the iodids, has marked nonspecific effects in the eye, which could be more widely utilized in the treatment of uveitis, episcleritis, tuberculous keratitis, and so forth. Ophthalmologists are all too unfamiliar with the effect of arsphenamin on interstitial keratitis, which is an immense advance over the effect of mercury, although it must be combined with it for permanence. The value of months and years of persistence in seemingly hopelessly impaired cases has been impressed on me.

Syphilis of the ear.—Deafness in hereditary or acquired syphilis should always be intensively treated, regardless of its duration. The occasional patient exhibits unexpected improvement (test it by speaking from behind the patient to keep him from reading lips). In acute onsets I prefer mercurial preparation, but I have seen no ill effects from

* For a critical consideration of the merits of this question see Kolmer.²³

arsphenamin. Patients with associated neurosyphilis may make an especially good response. Patients with positive Bárány reactions may make some objective improvement, but I believe the specificity of this response is still open to question.

Syphilis of the nose and throat.—The response to arsphenamin is miraculous and sometimes life-saving when deglutition has been obstructed, but if the process involves the larynx or trachea, the immediate use of this drug, even in seemingly trivial lesions, is dangerous because of the Herxheimer reaction. Provocative procedures must not be used in such cases. On the tongue the coincidence of lesions undergoing malignant changes and new crops of recurrences is possible. I have seen hemiglossectomy performed for carcinoma on gumma, while later because no treatment was given for the syphilis, another gumma was allowed to develop and degenerate on the other side. The confusion of the pathology of gumma with that of tuberculosis of the tongue (so-called tuberculoma) with a positive Wassermann reaction is more common perhaps than is realized.

SYPHILIS IN MOTHER AND CHILD

Syphilis in the mother* is one of the richest fields for prophylactic effort now available, as indicated by the steady influx of favorable reports of the work of obstetric services and prenatal care clinics,[†] in which the problem is beginning to receive the attention it deserves. Syphilis in the child should receive the same treatment as syphilis in the adult, in response to a growing appreciation that apart from stigmatization and the high mortality of untreated uterine infections, it presents no essential differences. In fact, the surviving untreated child has a resistance that is a valuable asset in treatment. Instead of boring you with a recital of technical details let me summarize what I conceive to be essential principles. The relative immunity of the woman from external manifestations of the disease and the suppressing effect of pregnancy and lactation has placed syphilis in women in a field by itself. The institution of therapy for the protection of the child seems to me justified in women in whom evidence of syphilitic infection is so doubtful that the advisability of treatment would be questionable under

* Skinner¹⁰ points out, however, how few women report for examination or treatment short of a fully developed infection.

† Williams¹¹ found 53 per cent syphilitic children of untreated mothers, 7.4 per cent of mothers treated during pregnancy.

other circumstances. The studies of Widakowich on spermatozoal anomalies and the findings of Eberson¹¹ in the male syphilitic furnishes the first tangible hint of direct paternal influence* and raises the question of whether or not the father should have treatment as a preparation for conception quite as much as the mother for gestation. This constitutes what I have both preached and practised as "treatment for life insurance" in the parents of a syphilitic child. Of late I have grown radical enough to believe that at no time can the woman who has had syphilis be advised to go through pregnancy without a treatment course coincidently. While this would bear hard on the mother of nineteen children, it need not be a hardship to the average family, and might, if observation of the children thus born should justify it, permit a relaxation of rules with respect to marriage.

Spirillicidal methods must be a prominent feature of the treatment of the pregnant woman, since a maximum destruction of organisms is, at least so far as our present knowledge goes, the best protection to the child. There seem to me to be good reasons for giving one-half to two-thirds of the full doses all around to the pregnant woman. Her infection is to some extent inhibited by her pregnancy,⁶ her liver and kidneys are both under strain, as evidenced by the familiar intoxications of pregnancy, and her metabolic and eliminative mechanism therefore cannot be equal to massive treatment.†

Whether the child born symptomless will remain so is the crux of the prophylactic phase of treatment in mother and child.‡ The possibility of long periods of latency after birth in children treated during uterine life, familiar in the untreated infection as well, demands the fullest development of facilities for the following up and observation of the syphilitic family before the cure of the child by treatment of the mother is accepted as established.

Systems of treating the child show a commendable trend toward increasing intensity, tempered by the realization that most uterine syphilis is late syphilis.⁴⁹ Fordyce and Rosen's advocacy of intramuscular arsphenamin is intended apparently to popularize the drug with

* Routh³⁰ makes an interesting argument for a paternal factor on the basis of Noguchi's spirillolysis, attempting also to explain delayed infection of the fetus in untreated cases.

† Adams¹ praises liberal doses of arsphenamin for mothers, but his mercurialization is practically all by mouth. Williams³⁶ does not specify his technic, but it seems to have been conservative.

‡ Much rather unguarded emphasis is being placed on the child's negative Wassermann test after birth.

those technically inexperienced.* I agree with Jeans that the expert seldom or never has need to use other than the intravenous route.† The tolerance of children for mercury is proportionately greater, I believe, than that of adults, and the intramuscular and inunction routes are gaining a well-deserved popularity. As a relief from the debilitating effects of prolonged mercurialization, arsphenamin is even more welcome in the treatment of children than of adults. The synergistic effect of the two drugs is also valuable in obstinate cases. Intraspinal measures have been effectively used.

The conception of the Weylander school-hospital for the combined treatment and education of children with heredosyphilis has not received the attention it should have in this country. The reports from the Scandinavian countries and Germany indicate that it solves the problems of hospital care and social rehabilitation.

CONCLUSIONS

This rather cursory review of the principles underlying certain special phases of syphilis will defeat its own purpose if it leaves the impression that the treatment of the disease should be parceled out in segments, each self-sufficient and governed by its own laws. Just as we are finding that early syphilis is no longer localized, even at the earliest appearance of the primary lesion, so we shall find as the intensity of our study increases that late syphilis does not begin in the first decade, but in the first hour. Preventing the transmission of the disease in its earlier stages and forestalling the individual tendency to complications, based on the peculiarities of the strain of parasite, the host, and the method of treatment, is the whole problem of syphilis. Forestalling implies detection, so that an increasing diagnostic alertness, a development of methods for detecting the earliest and not the late signs of pathologic change in vital organs and tissues, is not mere diagnosis, but a part of effective treatment. For all our so-called prophylactic effort, nothing will prevent the development of late complications in a certain group of patients who present the fatal combination of predisposed soil and tropic organism. It is equally true that an even smaller group of patients will master the infection for themselves, irrespective of our interference. Between these two extremes will come those whom we

* Adams¹ commends galyl in glucose, one-seventeenth of the adult dose.

† It would be interesting to apply the proportionally huge doses of neo-arsphenamin by rectum, employed by Mehrten,² to the treatment of difficult cases.

have radically cured, those whom we have managed to place in commensal relation to their infecting organism, those whose immunity we have broken by treatment measures whose potentialities for future harm as well as present good we do not yet understand, and those whom we have destroyed outright by treatment itself. The study of the interrelation of these groups is one of the most complex problems of the medicine of today. Its solution will not be accomplished by a mental or physical separation of the various phases of syphilis and syphilotherapy into air-tight compartments each with its own technic, ideals, and aims. Only that mode of approach will leave a significant impress on our future knowledge which envisages the entire disease, employs one or two methods in a large series of cases over a period of many years, records the results, and which, by lifelong observation and periodic complete reëxamination, detects impending serious pathologic change, and evaluates in detail and with accuracy the response of parasite and host.

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A MEMORANDUM ON THE OCCUPATIONAL STUDY OF SYPHILIS WITH SPECIAL REFERENCE TO FARMERS*

JOHN H. STOKES AND HELEN E. BREHMER

In January, 1919, the authors published¹ an account of a clinical investigation of syphilis in 100 railroad men examined in the Section on Dermatology and Syphilology of the Mayo Clinic. At this time it was planned to extend the work to similar clinical studies of syphilis made on the personnel of other occupations with a view to determining whether occupation as such could serve as a factor of predisposing or modifying influence in the course of the disease. With a view to securing a type of person whose mode of life was as different as possible from that of the railroad man, farmers were selected for the present group. A survey of 100 patients whose present and past occupation had been that of farmer or farm laborer has disclosed a very striking similarity between the two groups. In the tabulation the two groups of fifty railroad men each who comprise the first survey are compared with 100 farmers. The slightly lower incidence of frank neurosyphilis in the farmers and other minor variations among the various details of the statistical compilation are the only differences apparent. None of these differences is sufficiently marked to justify the conclusion that syphilis among farmers as seen at the Mayo Clinic differs in any essential particular from syphilis as seen in railroad men.

Two questions at once arise in the interpretation of such a result: (1) Were we in examining 100 farmers with syphilis really examining an occupational type of the disease? (2) Did we not merely examine a medically selected type of the disease in persons who because of the character of their symptoms and the relation of the medical profession to the general problem of syphilis inevitably gravitated to a diagnostic group for the final interpretation of symptoms whose anomolous character prevented a diagnosis by the general practitioner? On careful

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TABULATION—COMPARISON OF DUPLICATE SURVEYS OF TWO GROUPS OF FIFTY RAILROAD MEN EACH, AND ONE GROUP OF 100 FARMERS

	Railroad men.		Farmers.
	First series, per cent.	Second series, per cent.	Per cent.
Cerebrospinal fluid positive.....	64.0	79.0	51.7
Lues, central nervous system.....	79.5	83.0	68.5
Lues III, cardiovascular.....	18.7	20.0	12.0
Blood Wassermann negative.....	57.0	58.0	43.0
Blood Wassermann positive.....	43.0	42.0	50.0
Wassermann weak positive.....	4.0	2.0	7.0
Use of alcohol.....	75.0	61.0	55.0
Heavy drinkers.....	36.0	33.0	32.0
History of lues II unobtainable.....	62.5	60.0	60.0
Lues recognized at some time.....	55.0	57.0	
Age of onset late symptoms—over thirty.....	78.0	75.0	70.7
Gonorrheal history positive.....	80.0	73.0	52.0
Gonorrhea only.....	24.0	19.0	12.0
Symptoms appearing from six to twenty years after infection.....	71.0	67.0	46.0
Per cent infected by the age of 32.....	91.0	81.0	77.0
Wassermann on men under 25 will reach.....	70.0	60.0	61.0
Sterile or pathologic marriages.....	44.0	50.0	32.0 of 59
Age on entry—patients between 35 and 40.....	32.0	36.0	19.0
Concerned in operation of trains.....	76.0	70.0	
Concerned in operation of engines.....	36.0	36.0	

SYMPTOMATOLOGY

Gastric.....	28.0	22.0	25.0
Not suggestive of syphilis.....	18.0	24.0	8.0
Headaches and head pains.....	16.0	16.0	13.0
Cardiac.....	14.0	16.0	4.0
Diplopia and poor vision.....	14.0	10.0	16.0
Malaise, weakness.....	12.0	8.0	10.0
Shooting pains.....	10.0	20.0	19.0
Bladder (subjective).....	10.0	4.0	13.0
Nervousness.....	8.0	4.0	
"Do I have syphilis?".....	8.0	6.0	4.0
Laryngeal.....	8.0	6.0	4.0
Rheumatism.....	4.0	18.0	7.0
Ataxia (subjective).....	4.0	6.0	13.0
Girdle pain.....	4.0	4.0	16.0 (paresthesia)
Dizziness.....	2.0	8.0	13.0
Loss of consciousness.....		7.1	10.4

OBJECTIVE EXAMINATION

Abnormal knee reflexes.....	65.1	79.0	73.7
Abnormal Achilles reflex.....	78.1	62.0	61.9
Romberg positive.....	38.0	42.0	50.7
Speech defect.....	15.7	17.0	11.0
Mental symptoms.....	38.4	38.0	41.6
Paresthesias.....	55.8	51.3	41.0
Ataxia (objective).....	36.8	36.3	41.0
Bladder (objective).....	47.5	20.5	31.0

EYE FINDINGS

"Slow" reflexes.....	25.0 per cent of 48 cases—21.7 of 78 cases
Argyll Robertson pupils.....	37.0 per cent of 48 cases—32.0 of 78 cases
Unequal pupils.....	14.5 per cent of 48 cases—23.8 of 67 cases
Irregular pupils.....	14.5 per cent of 48 cases—26.8 of 67 cases
Muscular paralyses.....	12.5 per cent of 48 cases—10.5 of 67 cases
Fundus changes.....	26.5 per cent of 34 cases— 4.4 of 67 cases

consideration of these questions we have reached the conclusion that we were in all probability dealing with the general problem of the diagnosis of syphilis and especially of late syphilis and not with the peculiarities of syphilis in any special occupational type. In order to reach a correct interpretation of the possible modifications in the course of syphilis induced by occupational factors, the investigation must evidently be carried to the group and not be based on a study of that portion of the group which for one or another reason may be attracted to a center for medical examination.

The reaching of this conclusion does not for a moment invalidate the significance of our findings in those members of a given group whom we have examined. It is fully as important as ever for us to realize that railroad men with active neurosyphilis and with grave cardiac lesions are engaged in the operation of trains and in other work involving responsibility for the safety of the traveling public and the property of their employers. The farmer at his plow may fall a victim to cerebral hemorrhage with perhaps less serious consequences to the immediate physical safety of the public.

In the parallel columns presented in the table we have, therefore, a cross-section of syphilis as it is observed in a general diagnostic clinic such as that from which this material is taken. A number of the conclusions drawn from our previous papers may be drawn with equal reason from our study of farmers. The limited value of the history of infection and the blood Wassermann test in the diagnosis of the medical manifestations of the disease is again apparent. The masked onset of syphilis and gonorrhea falls to an average of 18 per cent. The slightly lower percentage of positive spinal fluids, and of neurosyphilis in the farmers is possibly due to the fact that taking the cases at random led to the inclusion of several more cases of primary and secondary syphilis among the farmers than among the railroad men. The conspicuous absence of a history of secondary manifestations in both groups seems to confirm the aphorism that the patient with severe secondary manifestations is fortunate rather than otherwise, since he is the only one

who receives enough treatment to protect him against late complications. The very striking correspondence of pupillary and neurologic findings in the two groups again points to the fact that the profession at large is not as yet utilizing to their full value the clinical ear marks of the disease produced by its encroachment on the nervous system.

CONCLUSIONS

1. A survey of syphilis in 100 farmers whose records were taken at random from the files of the section on Dermatology and Syphilology in the Clinic reveals no distinctive difference between the clinical picture of the disease in farmers and that in railroad men.

2. This result is not to be interpreted as precluding the possibility of special occupational types in the disease. For the determination of such types the investigation must be taken to the groups, instead of subjecting the group to a species of unconscious medical selection involved in resort to a diagnostic clinic.

3. The figures given in the table, therefore, present essentially the diagnostic problem of late syphilis in general medicine. They suggest further that physicians at large could profitably give less attention to the history of infection and the serum Wassermann test and more attention to the spinal fluid test and to the physical and especially the neurologic and ophthalmic findings in their effort to recognize late syphilis, and to interpret the medical picture presented by a given patient.

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A SCHEME FOR PRESENTING THE SUBJECT OF THE INFLAMMATORY DERMATOSES TO STUDENTS IN TERMS OF FUNDAMENTAL CUTANEOUS REACTION SIGNS*

JOHN H. STOKES

In 1914, while teaching histopathology of the skin to medical students at the University of Michigan, I found it necessary in developing a dynamic comprehension of the field to lay stress on the fundamental pathologic unity which underlies the seeming diversity in the clinical pictures of the inflammatory dermatoses. In order to accomplish this purpose I analyzed the clinical picture of inflammation of the skin into nine component elements or cutaneous reaction signs, erythema, edema, vesiculation, oozing, crusting, scaling, lichenification, fissuring, and hyperpigmentation. Each feature of the clinically visible picture had its counterpart in some feature of the histopathologic picture. Subsequently at the University of Illinois I used a similar device to impress on students the distinction between acute and chronic dermatitis, on which therapeutic decisions so often depend.

In 1918 and 1919, in my lectures to the Fellows in the Mayo Foundation, I expanded the original scheme into the present attempt to picture the fundamental morphologic and pathologic unity of the inflammatory dermatoses. The nine cutaneous reaction signs constitute a keyboard, so to speak, on which by varying degrees of emphasis on individual notes or elements the "tune" or basic structural motif of any one of the inflammatory dermatoses from simple dermatitis through urticaria and pemphigus to psoriasis or an exfoliative erythroderma, may be played. It was not, in fact, until I had attempted such a scheme that I really appreciated for my own experience the conception of a limited group of fundamental reactions which represent the response of the skin to a wide range of etiologic agencies. A demand for reprints of the charts from those who seemed to find this

* Reprinted from the Archives of Dermatology and Syphilology, 1921, iii, 641-647.

schematization enlightening and valuable in impressing on them the morphology and interrelations of the dermatoses in question has emboldened me to offer the idea for criticism and suggestions from other teachers of dermatology.

CHARTS

The nine clinical elements of an inflammatory process in the skin and their equivalents in the pathology are represented in Chart 1 in the order of their appearance as the process passes from an acute to a chronic phase. The effort must be to teach the student to identify the individual elements in his cases, to estimate their proportionate share in the clinical picture, and then, by a process of reasoning rather than of mere visual memorizing, to recognize the inflammatory character and name the type and the stage of the dermatosis. Chart 2 represents the application of the general scheme to the analysis of dermatitis, and aims to give the student at one and the same time a conception of the morphology of eczema and of its alignment with dermatitis in general. Subsequent charts carry the analysis into other types. In Charts 2, 3, 4, and 5 the relative importance of the individual morphologic elements in the clinical picture is represented by variations in the size of the type. The bold face is the most conspicuous or easily identified element in the dermatosis, the smallest type is the least conspicuous, or the rarest feature, or even entirely absent (such as vesicles in psoriasis). It will surprise a sophisticated dermatologist to see how seldom in his experience with such an analysis in mind even one of the nine elements will be found wholly and invariably absent from the clinical picture of any of the inflammatory dermatoses named. One has only to recall the description of vesicles in pityriasis rosea and urticaria pigmentosa, the clinical difficulty of distinguishing the Brocq type of parakeratosis variegata from premycotic mycosis fungoides, and the recently emphasized intermediate forms connecting urticaria with pemphigus by way of dermatitis herpetiformis, to realize, it seems to me, that the skin has only a limited range of reactions to a variety of pathogenic agents. These reactions manifest themselves in signs both clinical and pathologic, which when once identified by the student may form the basis of a rationalized physical diagnosis of cutaneous lesions. Such a mode of attack, even though imperfectly developed here, should be attractive to students because of its ability to introduce into a field, too often

subject to the desiccating influence of quibbles on morphology, some stimulating conceptions of fundamental unity and evolution.

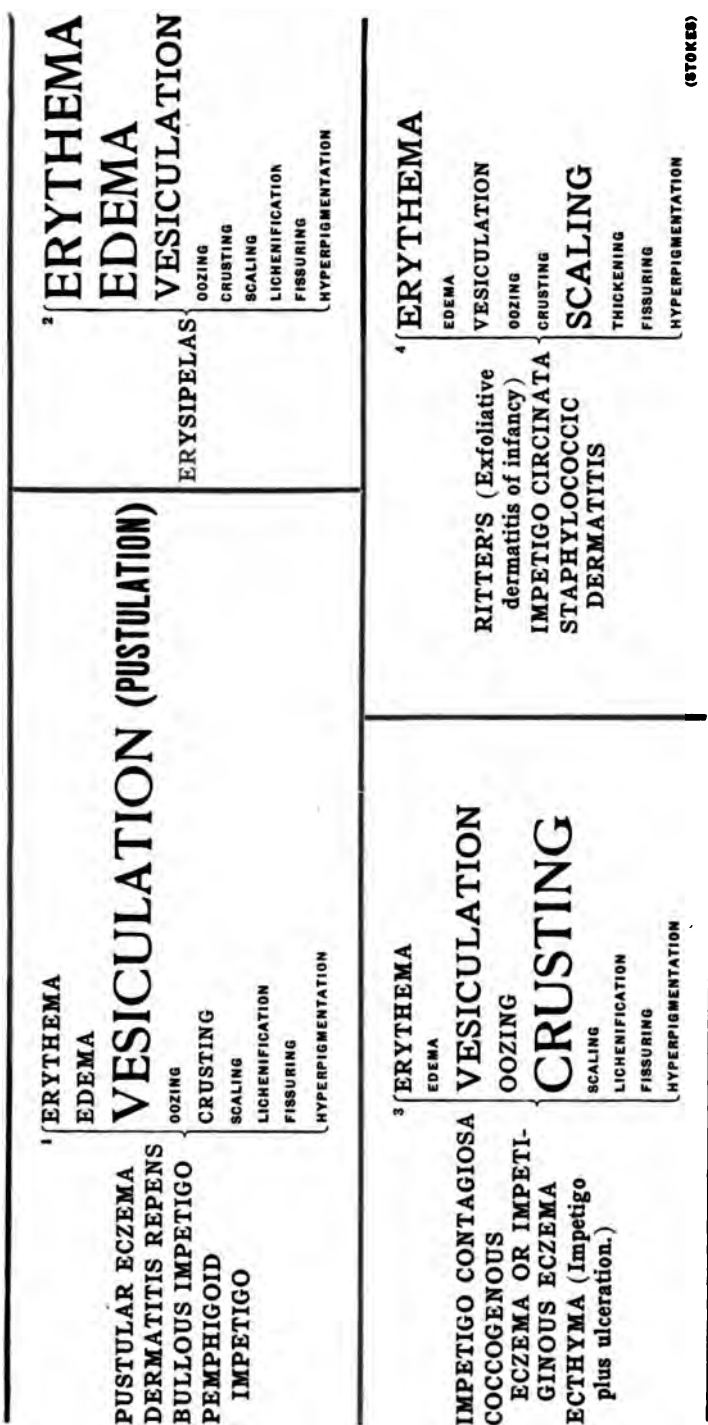
CHART 1.—A COMPARISON OF THE MORPHOLOGY AND PATHOLOGY OF DERMATITIS

HISTOPATHOLOGIC CHANGES		CLINICAL MORPHOLOGY (CUTANEOUS REACTION SIGNS)
1 Vascular dilatation.	A C U T E	1 Erythema.
2 Edema, inter and intracellular. Cellular infiltration.		2 Edema (intumescence, papule or plaque formation).
3 Vesicle and bulla formation 1-with rupture. 2-without rupture.		3 Vesiculation or bulla formation.
4 and 5 Exudation.		4 Oozing.
6 Disturbance of the keratization cycle. Acanthosis. Parakeratosis		5 Crusting from dried exudate.
7 Fibrous hyperplasia of cutis.	S U B A C U T E	6 Scaling.
8 Cracking (mechanical)		7 Thickening and lichenification.
9 Proliferation of melanoblasts. Appearance of chromatophores in cutis.		8 Fissuring.
		9 Hyperpigmentation.
	(STOKES)	
	C H R O N I C	

CHART 2.—ANALYSIS OF SIMPLE DERMATITIS

1 ACUTE DERMATITIS (I. & POISON IVY) ERYTHEMA EDEMA VESICULATION OOZING CRUSTING SCALING LICHENIFICATION FISSURING HYPERPIGMENTATION	2 SUBACUTE ECZEMA ERYTHEMA EDEMA VESICULATION OOZING CRUSTING SCALING LICHENIFICATION FISSURING HYPERPIGMENTATION
3 ACUTE ECZEMA ERYTHEMA EDEMA VESICULATION OOZING CRUSTING SCALING LICHENIFICATION FISSURING HYPERPIGMENTATION	4 CHRONIC ECZEMA ERYTHEMA EDEMA VESICULATION OOZING CRUSTING SCALING LICHENIFICATION FISSURING HYPERPIGMENTATION (STOKES)

CHART 3.—ANALYSIS OF DERMATITIS OF PYOGENIC ORIGIN OR COMPLICATED BY PYOGENIC INFECTION



(STOKES)

CHART 4.—THE TRANSITIONS FROM URTICARIA THROUGH ERYTHEMA MULTIFORME TO DERMATITIS HERPETIFORMIS AND PEMPHIGUS

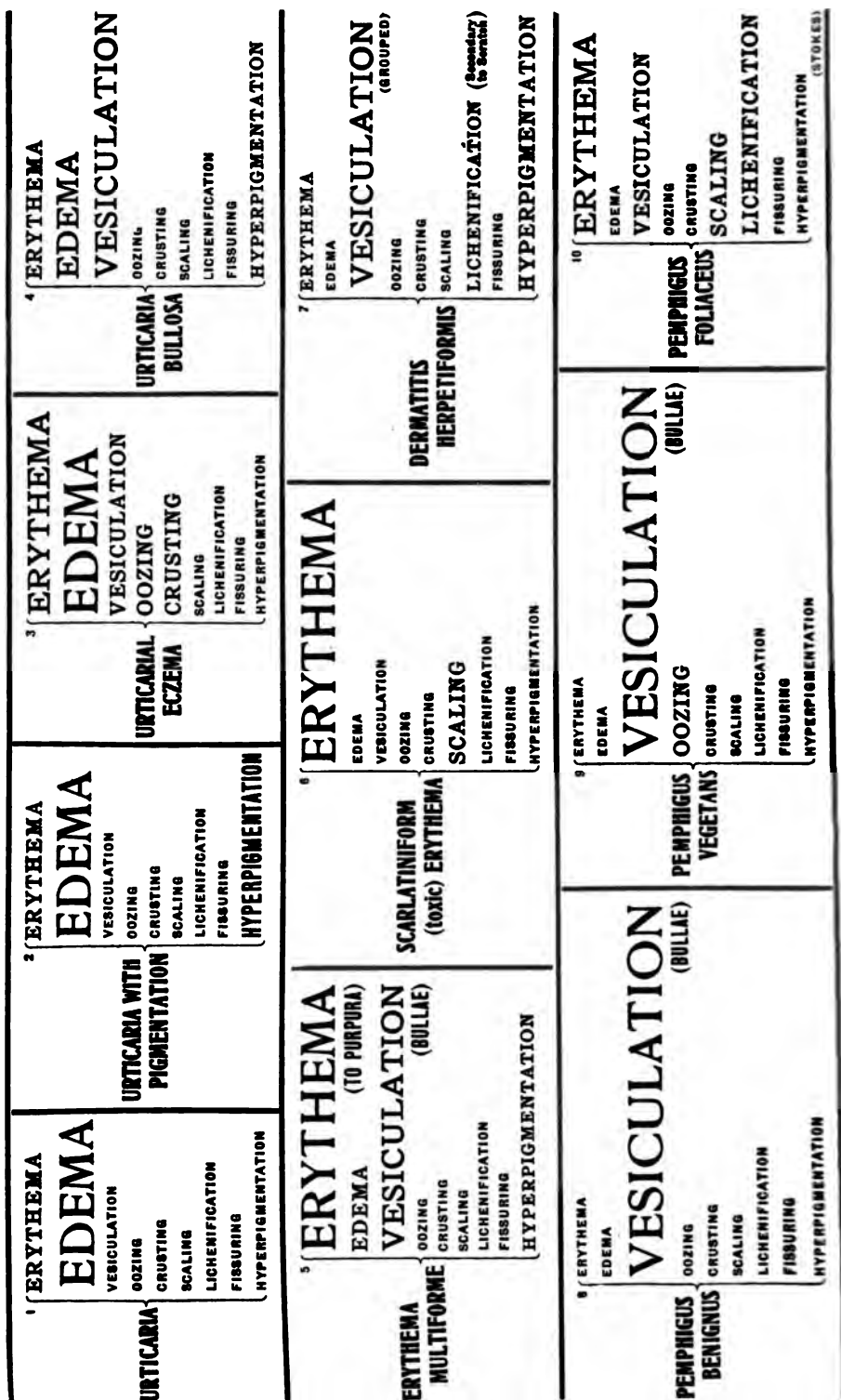


CHART 5.—ANALYSIS OF PSORIASIS, PARAKERATOSIS VARIEGATA AND THE EXFOLIATIVE ERYTHRODERMIAS

1 ERYTHEMA EDEMA VESICULATION OOZING CRUSTING SCALING LICHENIFICATION FISSURING HYPERPIGMENTATION PSORIASIS	2 ERYTHEMA EDEMA VESICULATION OOZING CRUSTING SCALING LICHENIFICATION FISSURING HYPERPIGMENTATION PARAKERATOSIS VARIEGATA
3 ERYTHEMA EDEMA VESICULATION OOZING CRUSTING SCALING LICHENIFICATION FISSURING HYPERPIGMENTATION PITYRIASIS RUBRA HEBRAE PITYRIASIS RUBRA PILARIS	4 ERYTHEMA EDEMA VESICULATION OOZING CRUSTING SCALING LICHENIFICATION FISSURING HYPERPIGMENTATION (STOKES) LEUKAEMIC AND PSEUDOLEUKAEMIC ERYTHRODERMIAS, (leukemids) PREMYCOTIC MYCOSIS FUNGOIDES

HEAD, TRUNK, AND EXTREMITIES

THE CHARACTER OF IRITIS CAUSED BY FOCAL INFECTION*

WILLIAM L. BENEDICT

That inflammatory lesions of the iris may be produced by the introduction of living bacteria into the blood stream has been demonstrated by several workers. Rosenow, in 1914, injected thirty-five rabbits with strains of organisms from patients suffering from rheumatism, and two of the thirty-five rabbits developed iritis. In 1915, he reported nine cases of iritis or iridocyclitis among forty-eight cases of lesions of the eye produced during the course of a long series of experiments in which animals were "injected intravenously under uniform conditions with streptococci from rheumatism, from appendicitis, from ulcer of the stomach, from cholecystitis, from erythema nodosum, from herpes zoster, from parotitis, from pyorrhea, from tonsils, and from dairy farm products."

Rosenow's experiments demonstrated that iritis occurs in animals as a local bacterial infection following bacteremia artificially produced. The experiments were not intended primarily to produce iritis, but to note what organs are affected when pathogenic bacteria isolated from suppurative foci in human beings are introduced into the blood stream and, further, to test the virulency of various strains of organisms after varying periods of growth on artificial mediums in the laboratory. If the ocular structures are affected by these organisms such affections, Rosenow believes, may be considered an indication of selective affinity for the ocular tissues. Rosenow found that organisms taken from persons suffering from rheumatism more frequently produce ocular lesions than organisms taken from persons suffering from any other diseases.

Brown and Irons, in recent experiments, produced iritis in rabbits by intravenous injections of streptococcus, *Bacillus mucosus capsulatis* (Friedländer), *Bacillus pyocyaneus*, and the gonococcus. They con-

* Reprinted from the Transactions of the American Ophthalmological Society, 1921, xix, 335-362.

cluded that "bacteria reach the eye by the circulating blood and can be recovered from the eyes of animals in which the iritis has been experimentally produced." In order, however, to produce iritis it was necessary to give large doses of the organism so that a condition of sepsis was created, and then it was produced only occasionally. In 1916, Irons, Brown, and Nadler conducted experiments "with the idea of discovering the changes in the power of an organism (*streptococcus*), which had already given rise to iridocyclitis in the patient, to produce similar lesions in animals, after varying periods of residence in the original host, of residence in animal tissues, and of growths on culture mediums." These experiments seem to have indicated "that the invasive power of the organisms for special tissues may change within a short period of time during residences in the original host, during animal passage, and in culture, without pronounced or constant changes in culture characteristics, or any general virulence for animals."

Lewis (1919) produced iritis in a rabbit by injecting into the blood stream a culture of *Streptococcus viridans* grown from a periapical infection in a patient suffering from acute iritis; the same organism was recovered later from a culture of a section of the iris of the rabbit. Lewis writes, "This experiment proves absolutely for the first time, as far as I know, the selective affinity of the organism found in dental root abscesses for the special structure which had been affected in the individual from which the tooth was taken."

Many clinical reports demonstrate the close connection between diseases of the eye and dental infection, tonsillar infection, rheumatism, and other infectious diseases. Since Lang, in 1913, published his opinion on the subject many published case reports have demonstrated the influence of dental sepsis on the eye. Very few of these reports were based on observations further than improvement of the ocular disease following the removal of diseased teeth and freedom from further attacks of iritis. Levy is reported to have said in discussing metastatic iritis, "No one, I believe, among all those investigating these metastatic eye infections, has been able to produce bacteriologic cultures from tissues taken from one of these eyes and only once has any body ever claimed to have produced an experimental iritis by animal inoculation."

It was my purpose in this investigation to determine whether organisms taken from a focus of infection, such as periapical infection of the teeth, or infection of the tonsils in patients suffering from acute or chronic iritis, have a selective affinity for the iris and whether the affinity

of the organisms is greater when taken from an individual during an acute attack of iritis. The experiments were conducted in the laboratory of experimental bacteriology of the Mayo Foundation. The cultures were made and the animals injected by Dr. E. C. Rosenow and by Dr. J. G. Meisser. Fourteen patients with iritis were selected as test cases. In order that the patient might definitely be considered a test case it was necessary to eliminate, so far as possible, by the history, the physical examination, and the laboratory tests, other causes of iritis, such as syphilis, gonorrhea, and tuberculosis. The method of collecting material from the focus and the cultural methods employed have been described by Rosenow.⁹ If a culture was to be obtained from an infected tooth, the tooth was removed under aseptic precautions, sterilized by flaming, the root cracked in a vise, and the pulp transferred to blood-agar plates and tall tubes of liquid medium. For purposes of animal inoculation the tubes with the growing organisms were shaken in order to insure thorough mixing and 2 c.c. of the fluid, containing usually 4,000,000,000 bacteria, were injected into a vein of the ear of a rabbit.

REPORT OF CASES

Case 1 (A267625). Miss A. E., aged twenty-four years, examined April 14, 1919, had suffered pain and lacrimation three days previously from a foreign body lodged in the left eye. The next day the eye became more painful. At the time of examination the palpebral and the ocular conjunctiva were injected. No trace of a foreign body could be found. The injection around the cornea gradually increased, the pupil contracted, and the pain became more intense. Iritis of the left eye developed and local treatment was instituted.

Roentgenograms of the teeth revealed four impacted molars (teeth 1, 16, 17, and 32, Fig. 221), and a fracture of the roots of both upper central incisors (teeth 8 and 9, Fig. 221), sustained eleven years previously. The impacted and fractured teeth were extracted and the sockets of the incisors curetted. The patient made a rapid recovery.

The pulp of the right upper central incisor was calcified; the pulp chamber of the left upper central incisor was enlarged and filled with foul smelling pus, and there was a small granuloma over its apex. Gram-positive diplococci, and a large number of fusiform bacilli and cocci of varying sizes, were identified in smears from the pus. A blood-agar plate of the pus produced a moderate number of indifferent colonies of staphylococci, but no green-producing or hemolytic streptococci. Cultures of the foul pulp in glucose-blood broth produced a diffuse cloud, due to short chained streptococci. A blood-agar plate of this culture showed green-producing streptococci in pure form. Cultures in glucose-blood broth, of the granuloma of this tooth, of a splinter of bone from between the two teeth, and of the calcified pulp of the right incisor, in twenty-four hours showed a diffuse cloud in the lower two-thirds of the tube, gradually rising to the top. The same type of streptococcus was isolated from blood-agar plates of the glucose-blood broth culture as from the foul pulp. Microscopic sections of the granuloma showed chiefly old dense fibrous tissue containing highly cellular areas of various sizes. The areas of infiltra-

tion contained fibroblasts, plasma cells, endothelial cells, arranged in rows resembling capillaries, and a moderate number of leukocytes. Gram stain of the fresh granuloma showed an occasional diplococcus, usually in or adjacent to the cellular areas of blood vessels. An area at the apex of the granuloma near a blood vessel contained a number of diplococci.

Primary glucose-blood-broth cultures of the foul pulp, of the calcified pulp, and of the granuloma, were injected intravenously into three rabbits. All had iritis and lesions of the nerve trunk, and one had lesions of the muscles. The first two rabbits (Rabbits 1699 and 1700) had marked lesions of the pulps and contiguous structures of teeth. The culture of streptococcus from the iris of one of the rabbits (Rabbit 1699) was injected into two other rabbits. Both developed lesions of the muscles, lesions around the pulps of the teeth, and in the dental nerves in the jaws. One of the five rabbits died from the injections; the others were anesthetized for examination in from three to six days.

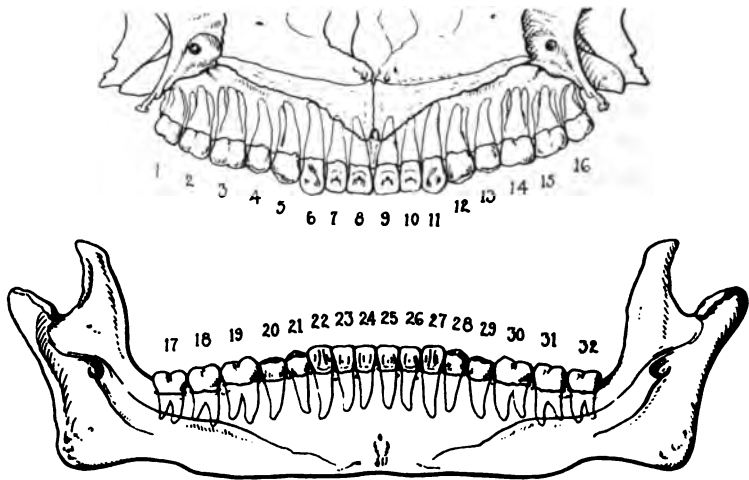


FIG. 221.—Diagram of plan for numbering permanent teeth for clinical references.

April 30, 1919, 9.00 a.m., Rabbit 1699, albino, weighing 1,100 gm., was injected intravenously with 3.5 c.c. of the glucose-blood-broth culture of the foul pulp. A small amount of sterile sand was added to a few drops of this culture and placed in the right conjunctival sac. At 8.00 p.m. the vessels of the iris and surrounding conjunctiva were congested, and both eyes were affected by lachrimation and photophobia. The rabbit seemed well otherwise. May 1, 7.00 a.m., the congestion of the vessels of the eyes was more marked (Fig. 222), and the animal appeared to be muscle-sore and inactive, with a tendency to crouch on its abdomen. The fluid in the anterior chambers was cloudy. At noon it appeared to be weaker; the congestion in the eyes had diminished. At 8.00 p.m. it jumped out of its basket in a convulsive seizure and died in violent convulsions fifteen minutes later. The circumcorneal congestion disappeared with death.

Necropsy was performed immediately. The iris of each eye was opaque and contained focal hemorrhages. The fluid in the anterior chambers was turbid. There were numerous hemorrhages of the posterior aspect of the iris and in the ciliary body (Fig. 223). The base of the appendix and the mesenteric lymph glands draining the appendix were swollen and hemorrhagic. There were marked degeneration of the myocardium, hemor-

rhages of the superficial muscles and aponeurosis around the thorax, punctate hemorrhages in the thymus, and numerous subendothelial hemorrhages in the septal wall in the



FIG. 222.—Iritis in Rabbit 1699 following injection of a culture from the foul pulp in a case of iritis (Case 1).



FIG. 223.—Reverse side of the iris shown in Figure 222.

left ventricle and in the papillary muscles. The parathyroid glands were extremely red, edematous, and swollen. The thyroid was hyperemic. In the first centimeter of the



FIG. 224.—Section of the ciliary body and iris of rabbit injected with the culture from dental pulp showing marked hemorrhage and infiltration. Methylene-blue and eosin ($\times 50$).

duodenum were a few small punctate hemorrhages; the mucous membrane of the cardiac end of the stomach was hyperemic. The lymph glands beneath the angle of the jaw and

ear and along both superior maxillary nerves were edematous and hemorrhagic; those in the axillary and inguinal regions were normal, and those in the popliteal spaces were hemorrhagic and edematous. The posterior tibial nerves were swollen and hemorrhagic. The periosteum opposite the right lower incisor was edematous and separated easily from the bone; the tooth was loose in the socket; the peridental membrane and the pulp were edematous and hemorrhagic. The corresponding inferior dental nerve was hemorrhagic and the pulps of a number of the molars on the right side were hemorrhagic and edematous. The pulp of the left lower incisor and the left inferior dental nerve were normal. The superior dental nerves were edematous and contained a few punctate hemorrhages. Smears from the hemorrhagic area in the periosteum and from three dental pulps showed



FIG. 225.—Section of the uvea of the eye of Rabbit 1699, shown in Figure 222, injected with a culture from the tooth in the case of iritis. Note the marked hemorrhagic and leukocytic infiltration. Hematoxylin and eosin ($\times 100$).

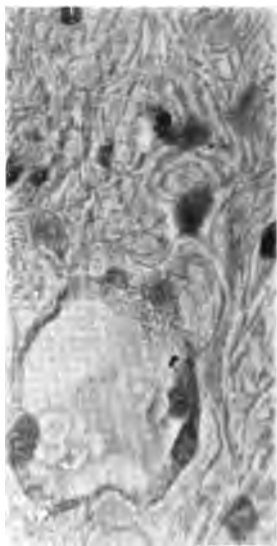


FIG. 226.—Diplococcus in capillary of hemorrhagic ciliary body.

gram-positive diplococci, but no other bacteria. Blood-agar-plate cultures of the blood, of the fluid from the anterior chamber, and of the pulp of the right lower incisor were negative. Glucose-blood-broth cultures of the tissue of the iris and of the pulp of the right lower incisor showed diffuse growth of a short-chained streptococcus, beginning at the bottom of the tube and gradually forcing its way to the top. Sections of the eyes showed marked hemorrhage and leukocytic infiltration of the ciliary body and iris (Fig. 224). Gram stains showed scattered diplococci in and adjacent to areas of hemorrhage (Figs. 225 and 226).

April 30, 1919, Rabbit 1700, a female weighing 1,720 gm., was injected intravenously with 5 c.c. of the glucose-blood-broth culture from the calcified pulp of the right upper central incisor. A few drops of the culture were mixed with sterile sand and dropped

into the right conjunctival sac. May 1, the animal appeared to be fairly well, but there were lachrimation and moderate congestion of the conjunctival vessels of both eyes. May 2, the eyes appeared to be normal, and the rabbit seemed well generally. It did not use the right hind leg, which it held up as if it were painful. Slight pressure along the sciatic nerve and posterior aspect of the legs seemed to cause pain. The joints were not swollen. May 3, the animal's condition was about the same, and chloroform was administered slowly; the animal went to sleep without a struggle.

The necropsy performed on this animal has been reported in full by Rosenow.⁹ No lesions of the iris were found.

Case 2 (A306110). Mr. S. S., aged thirty-two years, examined February 12, 1920, stated that he had had periodical attacks of inflammation in his eyes, more frequently in the left eye alone, one each year for the past eight years. The attacks seemed to come on when he had a cold and did not leave until the cold disappeared. The last attack began January 1 with itching of the eyelids followed by photophobia. He had had serum vaccine injections.

Vision of the right eye was 6/7 +3, in the left eye 6/6. The left eye was kept closed, and the lids were red. There was a marked ciliary injection. The pupil was moderately dilated and reacted slightly to light and in accommodation. The anterior chamber was normal in depth. Intra-ocular tension was normal to touch. The iris was ragged about the pupillary margin and there were pigment deposits on the lens. Transillumination revealed moderate atrophy of the iris. The fundus was best seen with a -9 lens.

The tonsils were found to be size 3 on a scale of 1 to 4, and to contain plugs. Four teeth (3, 14, 29, 30) showed evidence of periapical infection (Fig. 221). Two analyses of urine were negative except for a few pus cells. The leukocytes numbered 12,000; a differential count of 200 cells revealed polynuclear neutrophils 73 per cent, small lymphocytes 16.5 per cent, large lymphocytes 10 per cent, and basophils 0.5 per cent.

February 25, teeth 14, 29, and 30 were extracted. March 3, teeth 17 and 20 were extracted.

Cultures were made of a granuloma from the upper left first molar. A pure culture was obtained of *Streptococcus viridans* in short chains, as diplococci, and a few long chains. Two cubic centimeters of a broth culture were injected into an ear vein of a rabbit. Two days later the rabbit appeared to be very sick (the day of injection the rabbit was so wild he could hardly be caught), it crouched down low, its head drooped, and its eyes, which were kept half closed, showed some lachrimation and circumcorneal congestion. The following day the iritis was well advanced. The photophobia and lachrimation were increased; the irises of both eyes were congested, and the circumcorneal congestion was more intense than on the previous day. The animal appeared to have sore muscles. It died the fourth day after the injection. At necropsy two large hemorrhagic areas in the quadriceps extensor muscles of each hind leg were found, and a periosteal lesion in the region of the lower left incisor. The appendix was highly inflamed. In the stomach were several small hemorrhagic lesions, and a few larger ones, about 2 to 3 mm. in diameter, which were beginning to ulcerate. A pure culture of *Streptococcus viridans* was obtained from each eye.

Case 3 (A311972). Mr. T. M. F., aged thirty-eight years, came for examination April 12, 1920 because of attacks of iritis in the right eye. He stated that he had had attacks of rheumatism on an average of two a year for the past ten years; the first attack followed his being struck in the eye by a small piece of steel and lasted four weeks. The last attack had begun three weeks before examination.

Vision in the right eye was 6/5, in the left eye 6/4 without glasses. The right pupil was slightly smaller than the left. The intra-ocular tension of both eyes was normal.

There was well marked ciliary injection about the right limbus. The cornea was clear, the anterior chamber deep. The iris was off color, but not markedly congested. The general examination was practically negative. The adenoids had been removed, but not the tonsils. The urine was negative. The leukocytes numbered 10,200. The serum Wassermann test was negative.

The dental examination revealed two infected teeth, the upper right first bicuspid, tooth 13 (the pulp of which was still slightly vital), and a lower left second bicuspid, which showed evidence of disease in the roentgenogram. Teeth 13 and 20 were removed by alveolar resection April 15. Cultures from tooth 13 showed pure colonies of *Streptococcus viridans*.

April 16, 1920 at 10.00 a.m., Rabbit 83 was injected intravenously with a culture from the upper right first bicuspid. At 8.00 p.m. the lids of both eyes were stuck together by dried secretion; circumcorneal congestion was marked in both eyes. At 9.30 p.m. the irises of both eyes were extremely congested and contained numerous small hemorrhages; the pupils were contracted, measuring 3.5 by 5 mm.; photophobia was marked. Large periosteal lesions were found on the inner aspect of left tibia and a definite periosteal lesion opposite the apical third of the lower left incisor. Cultures were made from the iris, from the fluid in the anterior chamber of the eyes, and from the joint fluids. Pure culture of *Streptococcus viridans* was obtained from each place.

April 16 at 8.00 p.m., Rabbit 84 was injected with a culture from the granuloma of the lower second bicuspid, and Rabbit 85 with a culture from the upper right first bicuspid. Both rabbits had slight iritis at 12.00 midnight, and the next morning at 8.00; it disappeared gradually during the day.

April 17, Rabbit 90 was injected into the anterior chamber of the right eye with a culture made from the fluid from the anterior chambers of the eyes of Rabbit 83. The injection was made with a small pipette. The next day marked lacrimation and congestion of the vessels of the left eye, decided photophobia, and swelling of eyelids were observed. The coats of the right eye was injected deeply and the fluid in the anterior chamber was turbid. The rabbit was chloroformed.

At necropsy the scleral coat of the right eye was quite hemorrhagic and infiltrated; the cornea was much thickened, but the vitreous was clear; the vessels of the iris were markedly congested; the iris was moderately edematous, but it was not covered with exudate; the fluid in the anterior chamber was slightly turbid. Many small hemorrhages were found in the muscles and periosteum, especially on the inner aspect of the right tibia and along the internal popliteal nerves, and a number of hemorrhages in the lower portion of the left tibialis anticus. Opposite the roots of both upper incisors were hemorrhagic, edematous areas. The pulps of both lower incisors were extremely congested and hemorrhagic. Cultures made from the iris, the fluid in the anterior chamber of the eyes, the muscle lesions, the joint fluids, and the pulps of the lower incisors showed pure cultures of *Streptococcus viridans*.

April 17, a culture made from the iris of Rabbit 90 was injected into the anterior chamber of the left eye of Rabbit 94. The following day the marked lacrimation and congestion of the vessels of the left eye were followed by much swelling, and the fluid in the anterior chamber of the eye was turbid, almost pus-like in appearance. May 1, the rabbit was killed by chloroforming. Cultures made from the uninjected eye as well as from the injected eye showed pure colonies of *Streptococcus viridans*. Cultures from the joint fluid also showed *Streptococcus viridans* in pure culture.

May 2, Rabbit 104 was injected intravenously with cultures from the iris of Rabbit 94. Two days later the rabbit showed severe iritis in both eyes, marked congestion of the vessels of the conjunctiva, circumcorneal injection, and turbid fluid in the anterior chambers of the eyes. The rabbit was definitely muscle sore. The following day the condi-

tion was more marked. The congestion of the vessels and the circumcorneal injection were greater. The fluid in the anterior chamber, especially the lower half, contained a large amount of flaky pus.

Necropsy revealed many muscle lesions, particularly around the joints and the anterior and outer aspects of the left and right tibias. There was a slight area of infiltration over the upper left incisors, but no lesions in the viscera. The knee joints and the ankle joints contained a moderate amount of turbid fluid. Cultures from the iris, the fluid of the anterior chambers of the eyes, the muscle lesions, and the joint fluid contained short chained streptococci and diplococci (*Streptococcus viridans*).

Case 4 (A314223). Mr. W. L. J., aged forty-seven years, was examined April 30, 1920 because of poor vision, which was reduced to 1/60 in each eye. Because of the deafness of the patient which followed measles at the age of four and his speech defect it was difficult to obtain a clear history. About twenty years before examination he had had some difficulty with the eyes, but they recovered and were well until the last four years when following an inflammation in both eyes vision failed gradually. An operation was performed on the right eye at that time. The patient had had rheumatism in the right shoulder and knee for the past year with swollen and stiff joints.

On examination the right eye was found to have a slight ciliary injection at the limbus, corneal nebulous opacity, and some vascularity, superficial and deep, of the cornea. The anterior chamber was of moderate depth, the iris slightly off color. There was a broad surgical coloboma of the iris on the nasal side. In the left eye were well marked nebulous opacities of the cornea and a dull and lusterless iris. Ophthalmoscopically in the right eye there was a red reflex in the coloboma; the fundus details were not made out. In the left eye no red reflex could be seen with the ophthalmoscope, but by transillumination a red reflex was seen through the pupil. The iris was very thin and atrophic.

The patient's tonsils had been cleanly removed. He had a marked eighth nerve atrophy. The bone conduction was reduced. The urine was negative. The hemoglobin was 85 per cent; the leukocytes were 7,600. The Wassermann test on the serum and on the spinal fluid was negative. The Nonne reaction was negative. Two lymphocytes were found in 1 c.c. of spinal fluid. Teeth 3, 10, and 19 showed periapical infection. Tooth 32 was impacted (Fig. 221).

May 26, 1920, teeth 3, 10, and 19 were removed.

May 26, 1920, a pure culture of *Streptococcus viridans* was obtained from a granuloma of tooth 19 and injected into a rabbit. Two days later the rabbit showed slight iritis, more definite in the left eye than in the right eye. There was some circumcorneal injection. The following day the rabbit's eyes were again normal. No further injections were made. The rabbit was kept under observation for several weeks, but further symptoms did not develop and the animal was not sacrificed.

Case 5 (A315896). Mr. J. R., aged twenty-four years, was examined May 13, 1920. He stated that until the age of twelve his sight had been normal; since then it had gradually failed, more rapidly during the past year. Since the age of three he had had considerable rheumatism affecting the hands, feet, and hips, but not the eyes. He had had no trouble with his eyes except occasional attacks of soreness for three or four days, but they had no direct relation to his rheumatism. He remembered having measles, but no other children's diseases.

Vision of the right eye was 3/60, of the left eye 2/60. The eyes were normal in size, and rotated normally in all directions. Convergence was weak, but under special test convergence could be obtained. In the right eye the palpebral conjunctiva showed a moderate injection and there was some injection of the ocular conjunctiva in the palpebral fissure on either side of the cornea. The iris was bluish gray. The pupil was centrally placed, 2 mm. in diameter, and it reacted to direct and consensual light and in accommo-

dation. The left eye showed some conjunctival injection. The cornea was small, barely 11 mm. in diameter. Just inside the limbus at 9.00 was a greenish elevated area 1 mm. wide and 2 mm. long, situated entirely on the cornea free from the limbus. The entire cornea was hazy. The iris was greenish gray. The pupil was 1.5 mm. in diameter and reacted to direct and consensual light and in accommodation. The tension in both eyes was normal to the finger touch. The right pupil was dilated to 2.5 mm. by instillation of one drop of cocain solution and with a +16 lens the iris was seen to be bound down to the lens capsule by numerous synechia. There were many pigment deposits on the lens capsule. The fundus could not be seen in the right eye. In the left eye was a fine stippling of the posterior surface of the central portion of the cornea. The balance of the cornea was clear. The iris was bound down to the lens. There were numerous pigment deposits on the lens and a thin white veil over the pupil. The condition of the mediums behind the opening could not be ascertained. Atropin solution failed to cause full dilatation of either pupil.

A general examination revealed fibrous tonsils size 2 and chronic tonsillitis. The hemoglobin was 77 per cent, the erythrocytes were 4,700,000, and the leukocytes 7,100. The Wassermann test on the serum was negative. Periapical infection was found of teeth 4, 13, and 40 (Fig. 221). Chronic rheumatism, myocarditis, and endocarditis were found.

May 21, the infected teeth were removed. The tonsils were removed May 24.

May 30, the vision of the right eye was 2/15, of the left eye 6/100.

May 24, one rabbit was injected intravenously with a culture from the tonsils, and two rabbits with cultures from the granulomas. Symptoms did not appear in the rabbits and they were not sacrificed.

Case 6 (A317695). Miss L. G., aged eighteen years, was examined in the Clinic May 29, 1920. In September, 1918, she had received a rather severe blow on the head and two days later she saw spots before the left eye. She was told by an oculist that the spots were due to a hemorrhage in the left eye. The vision was very much reduced, but after two weeks of treatment the vision was almost fully restored. She had no further trouble until January, 1920, when she again noticed spots before the left eye and the vision of the left eye gradually failed. She was under treatment by various specialists without improvement.

The right eye was found to be normal. The ocular conjunctiva of the left eye was injected around the cornea. The cornea was staphylomatous. The entire surface of the cornea was finely stippled like an orange peel. The entire cornea was hazy, the posterior surface covered by small white dots. The anterior chamber was deep; the iris was light brown, muddy, and faded, receded, and funnel shaped. The pupil was 4 mm. in diameter and did not react to stimulus. The eye could be transilluminated clearly in all directions. No definite deposits could be seen on the capsule of the lens.

Wassermann tests on both the blood and spinal fluid were negative. The urine was negative. The blood count and hemoglobin were normal. The sinuses were not infected. The teeth were normal except for a suspected bad root of an upper right incisor shown by a roentgenogram. There was a faint general reaction under 0.3 mg. of tuberculin, but there was no focal or local reaction. The tonsils were size 2, with plugs which contained green-producing streptococci, staphylococci, and gram-positive bacilli. The nose and ears were negative. A roentgenogram of the chest was negative. No evidence of infection was discovered except in the tonsils and in teeth 10 and 20 (Fig. 221).

The tonsils were removed June 10, 1920. The infected teeth were removed June 21, 1920. A large growth of green-producing streptococci and a few staphylococci were obtained from the material around the roots of the teeth. Two rabbits were injected with these cultures, but no symptoms developed. The rabbits were necropsied a few days after their injection, but only a few muscle lesions were found.

Case 7 (A320901). Mr. J. G., aged fifty-four years, was examined June 23, 1920. His first attack of iritis had been in the left eye in 1907, and had lasted two weeks. The pain was controlled by aspirin. In 1910, an attack of very painful iritis in the same eye lasted six weeks. A few days after this had subsided, the right eye became affected. Since then he has suffered at least thirty attacks, two very severe and six severe. Since 1910, he had had a divergence of the left eye. Since 1911, he had been having pains in the back, more frequently during cold weather. His tonsils had troubled him somewhat. He had had gonorrhea in 1889 followed by cystitis, no venereal infection since.

The vision of both eyes was 6/4. There was a divergent strabismus of 20 degrees. The pupil of the right eye was normal in size and position, but irregular; its margins were free. It reacted to direct and consensual light stimulation. The fundus was normal. The anterior chamber of the left eye was shallow, the iris steel gray. There were synechia below from 5.00 to 8.00. The upper pupillary margin was free. The pupil dilated upward and reacted to direct and consensual light stimulation. There were large floating opacities in the vitreous; the mediums were otherwise clear.

The tonsils were size 2; they did not contain pus. The nose appeared to be negative. The urine was negative. A Wassermann test on the serum was negative. A roentgenogram of the teeth showed periapical infection of teeth 4, 13, and 19 (Fig. 221). The genito-urinary tract was negative except for a slight enlargement of the prostate.

June 29, 1920, the three infected teeth were removed and cultures made from the infected material around the roots. A large growth of green-producing streptococci and a few staphylococci were obtained. One rabbit was injected with the culture. No symptoms developed, so the rabbit was not sacrificed.

Case 8 (A322553). Mr. W. L. C., aged forty-six years, was examined June 30, 1920. His first attack of iritis had occurred fifteen years before in the left eye. Since then he had had seven attacks in the left eye and two in the right eye.

The eyes were quite sensitive to light. Vision of both eyes with correction was 6/4. The right pupil was 4 mm. in diameter, the iris brown, and the markings not obscured. The pupil dilated evenly after the instillation of cocain solution in the conjunctival culdesac. There was an eversion of iris pigment on the pupillary margin corresponding to 3, 7.30, and 8.00. On the anterior surface of the lens in the pupillary area was a small ring of pigment deposit. The mediums were otherwise clear. The fundus was negative. The pupil of the left eye dilated evenly after instillation of cocain solution in the conjunctival culdesac. There was no synechia or deposits of pigment on the lens.

The general examination was negative except for small tonsils which contained fluid pus. Two examinations of urine were negative. The hemoglobin was 76 per cent; the erythrocytes were 4,840,000; the leukocytes 4,800. The Wassermann test on the serum was negative. All of the patient's teeth had been extracted. Roentgenograms of the chest and colon were negative. Some infection in the upper alveolar process was suspected.

July 6, a radical resection of the upper alveolar process was performed. Cultures were not made. July 15, the tonsils were removed.

Cultures were made from the pus taken from the tonsils before operation and after operation. Green-producing streptococci and a few staphylococci were obtained. Two cubic centimeters of the culture in glucose-brain broth were injected intravenously into each of four rabbits. Symptoms of iritis did not develop in the rabbits. After several days of observation all the rabbits were necropsied. One rabbit had hemorrhagic lesions in the endocardium. Lesions were not found in the other three.

Case 9 (A326969). Mrs. J. S. W., aged twenty-nine years, was examined July 28, 1920. When she was ten or twelve years old she had an attack of inflammation of the eyes which lasted all summer. She had had no further disease of the eyes until two months before, May, 1920, when an inflammation of the left eye was followed by ulcera-

tion of the cornea. This attack lasted one week. Two weeks later she had another attack in the same eye. Shortly afterward she had a similar attack in the right eye followed by ulceration of the cornea. The attack from which she was suffering at the time of examination had lasted three or four weeks during which she had been under constant treatment.

Vision of the right eye was 6/7. Vision of the left eye was not obtained because of photophobia and the patient's objection to attempt to use the eye. A small infiltrated area on the cornea was stained with fluorescein; near by was an ulcerated area with vessels running over the limbus toward it. Local treatment was instituted and a search made for focal infection.

On general examination chronic tonsillitis and dental infection were found. The tonsils were size 3 and contained a small amount of pus. The urine was negative. The hemoglobin was 73 per cent; the erythrocytes were 4,000,000, the leukocytes 10,800. The Wassermann test on the serum was negative on three occasions. A roentgenogram of the chest was negative. Evidence of genito-urinary infection could not be found. The cervix was soft, since the patient was five months pregnant. A roentgenogram of the teeth showed infection of teeth 4, 5, 18, 30, and 31 (Fig. 221).

August 3, teeth 3 and 5 were removed.

August 8, the patient was dismissed. The left eye was comfortable. There was a very slight circumcorneal injection. The upper outer quadrant was rather hazy, but well epithelialized.

August 23, 1920, the patient returned to the Clinic with another attack of iritis in the left eye. Lacrimation and photophobia were marked. The lids were moderately swelled. The palpebral conjunctiva was congested. Local treatment was instituted and August 30 the remaining infected teeth were removed under block anesthesia. The patient was discharged August 31, at her own request, to resume treatment with her home physician.

One culture was made from a tooth in which the pulp was dying, and another from a tooth which showed evidence of infection in the roentgenogram. Green-producing streptococci (short chains and diplococci) and staphylococci grew in the cultures. Three rabbits were injected. Twenty-four hours later the eyes of one rabbit were inflamed, and the iris of each eye was congested and contained several small hemorrhages. The following day the rabbit died. The type of organisms injected in pure culture were recovered by culture from the fluid of the anterior chamber of each eye and from culture of bits of tissue of the iris dropped in a tube of medium. The same strains of organisms were also recovered from the blood of the animal immediately after death. The other two rabbits injected with the same cultures failed to show symptoms and were not sacrificed.

Case 10 (A327736). Mrs. H. C. E., aged forty-nine years, was examined August 3, 1920. In May, 1920, the patient thought there was a foreign body on the cornea of the left eye and an attempt was made to locate and remove it. A foreign body could not be found, but the search for it resulted in irritation of the eye. Both eyes became badly inflamed and painful, requiring the services of an oculist. The patient was referred to me by her physician. She brought a letter from her oculist giving in detail her history and his findings. The examination and treatment before coming to the Clinic had been well carried out. She had had a serum Wassermann test which was negative. Her tonsils had been removed July 15, 1920, and were reported to be septic. Two teeth which had been removed were reported to have had abscesses at their roots. Following the removal of the teeth and tonsils, there was an apparent remission of the ocular symptoms, although the patient was unable to use her eyes for her housework because of photophobia and pain.

On the patient's admission to the Clinic she had signs and symptoms of chronic iridocyclitis. The vision of the right eye was 6/12, of the left eye 6/60. Photophobia and

lacrimation of the left eye were marked. The lids were swollen, scarred, and wrinkled from applied heat. The palpebral conjunctiva was deeply congested and there was an injection of the ocular conjunctiva, more marked at the limbus. A well defined and deep scleral blush completely surrounded the cornea, which was hazy from thickly studded deposits on its posterior surface and infiltration of the middle layers. The anterior chamber was normal in depth, the iris dark slate gray, with blurring of the finer markings. The pupil was 6 mm. in diameter, round, and with numerous posterior synechia. Atropin solution could not be used because of the violent reaction. Neither hemorrhages nor large vessels could be seen on the iris. The lens was covered with small pigment deposits in the pupillary area. The pupil did not react to direct light. Only a dull red reflex from the fundus could be seen with the ophthalmoscope. The intra-ocular tension was normal to touch. The right eye was quiet except for lacrimation and some photophobia when the left eye was exposed. The right cornea was clear, but the iris was thickened, the lens covered with pigment deposits in the pupillary area. The mediums were otherwise clear and the fundus normal. The intra-ocular tension of this eye also seemed to be normal to touch. A few gram-positive streptococci, staphylococci, and gram-negative bacilli were found.

A general examination was made in order to discover the cause of the iritis. The urine on three occasions was negative except for occasional erythrocytes and occasional pus cells, an interesting finding in the light of later revelations. The hemoglobin was 75 per cent; the erythrocytes were 4,680,000, the leukocytes 10,000. A Wassermann test on the serum was again negative. The patient had right and left nephrolithiasis with atrophy of the right kidney. The tonsils had been cleanly removed and no pus could be found around the ears and nose. The teeth were negative except for three questionable teeth, 3, 6 and 11 (Fig. 221), which were later removed and found to have infection around the roots.

In the belief that the right kidney had something to do with the condition of the eyes, a right nephrectomy was performed October 23, 1920 by Dr. W. J. Mayo, who reported "kidney contains stones, infected." The day following the operation the left eye became very painful and a marked circumcorneal injection with increased haziness of the iris developed. Three days later the inflammation had almost subsided. The patient was very comfortable and the eye quiet until November 8. Then the eye was not quite so well and November 10 was very much more uncomfortable than it had been for several days. Local treatment was continued, but the last observation made December 7 showed the eye to be irritable with some photophobia and lacrimation. Healing of the nephrectomy wound was delayed so that the side was draining for more than three months.

Cultures were made from the wound and injected into rabbits several times. Cultures were made from the teeth and from the wound, and one rabbit was inoculated intravenously. In the cultures made from the infected teeth large numbers of green-producing streptococci and a few staphylococci were obtained. The rabbits did not show symptoms, so were not sacrificed.

Case 11 (A331185). Mr. E. A. M., aged forty-three years, was examined August 24, 1920. He complained of attacks of iritis for the past thirteen years. He stated that he had had attacks in both eyes, more often in the right eye than in the left, and that only one eye was affected at a time. The last attack was seven or eight weeks previous to his examination in the Clinic. He had always had local treatment during the attacks. His tonsils had been removed three years before, but the attacks of iritis had recurred since then. One tooth had been removed three years before and one three weeks before.

On examination it was found that vision of the right eye was 6/60 and could not be improved by glasses, vision of the left eye was 6/20 and could not be improved with glasses. The cornea of the right eye was clear. The anterior chamber was normal in

depth. The iris markings were perhaps slightly muddy, the pupillary margin slightly irregular. The pupil was 3 mm. in diameter and reacted a trifle sluggishly. By oblique illumination iris movement was observed around the lower three-fourths of the pupillary margin, although a rather firm adhesion with plastic exudate bound the iris to the anterior surface of the lens. The vitreous was clear, the fundus negative. The cornea of the left eye was clear, the iris of good color; the pupil was slightly irregular, about 3 mm. in diameter, but it reacted normally. By oblique illumination old exudates and pigment deposits were visible in the pupillary area on the lens capsule. The fundus was negative.

A general examination was negative except for evidence of periapical infection in teeth 1, 10, and 30 (Fig. 221). The urine was negative; the hemoglobin was 80 per cent; the leukocytes were 9,200. A serum Wassermann test was negative. The genito-urinary examination was negative also.

August 31, 1920, the infected teeth were removed and one rabbit was injected intravenously with a culture of green-producing streptococci and staphylococci from the infected tissue around the roots. No symptoms were observed in the rabbit from the injection, and the animal was not sacrificed.

Case 12 (A333100). Miss P. H., aged twenty-two years, was examined September 7, 1920. For the past six or seven years she had noticed a gradual loss of vision of both eyes unaccompanied by inflammation or pain. She had had the eyes examined a number of times and had been told that she had uveitis. The vision had failed more rapidly during the past three years. Examination of the right eye revealed little change. The iris was of good color, the pupil round, about 3 mm. in diameter, and it reacted normally. In the left eye the iris was decidedly muddy, the pupil eccentric, and the margins irregular and adherent to the anterior surface of the lens in the superior temporal quadrant. The pupillary reactions were sluggish.

By ophthalmoscopic examination of the right eye deposits were found on the posterior surface of the cornea; the pupillary margins were irregular; there was a moderately dense opacity at the posterior pole of the lens, and large floating vitreous opacities. The disc had a rather pronounced pallor with considerable blurring and loss of detail. In the left eye the pupil was bound down almost completely by a posterior synechia. There was a clover-leaf-shaped opacity in the posterior part of the lens, and floating vitreous opacities. Fundus details were blurred, but the disc appeared to be of normal color. The vision of the left eye was 6/7, of the right eye 6/5 with correction. The diagnosis was chronic uveitis of the left eye.

On general physical examination the patient was found to be well developed and well nourished, but with acne vulgaris over the skin of the back. The urine was negative. A serum Wassermann test was negative. The tonsils had been cleanly removed in 1916; the nose had a slight deflection of the septum; the ears were negative. A roentgenogram of the teeth showed apical infection of tooth 4 (Fig. 221).

September 15, 1920, tooth 4 was extracted and cultures made from the infection around the root. Large numbers of green-producing streptococci and a few staphylococci were obtained. One rabbit was injected intravenously with the culture, but it failed to develop symptoms, so it was not sacrificed.

January 31, 1921, the patient was again examined at the Mayo Clinic. There was no change in the condition of the left eye.

March 12, 1921, there was a painful superficial keratitis accompanied by marked photophobia and lacrimation. There was a mild iritis also.

Case 13 (A340150). Mrs. O. S., aged twenty-six years, was examined November 8, 1920. The previous eye history was negative. The patient had an iritis in the left eye which had started five weeks previous to her examination at the Mayo Clinic. At the

time of the examination the vision of the right eye was 6/4, of the left eye 6/60. A general examination revealed a benign tumor of the left breast. The blood pressure was normal. Two tests of the urine made two months apart were negative. The hemoglobin was 75 per cent; the leukocytes were 5,000. A roentgenogram of the chest was negative. A serum Wassermann test was negative. The tonsils had been cleanly removed. The nose, sinuses, and ears were negative. A roentgenogram of the teeth showed three teeth (18, 19, and 20) with periapical infection.

November 30, 1920, the infected teeth, 18, 19, and 20, were removed under block anesthesia, and cultures made from infected material about the roots. Green-producing streptococci and a few staphylococci were obtained. Two rabbits were injected intravenously. No symptoms appeared in either rabbit after the inoculation, so they were not sacrificed. December 1, 1920, the vision of the right eye was 6/4, of the left eye 6/12. The ciliary injection had disappeared. The pupil, no longer under atropin, was active. With correction, sphere +.75, the vision in the right eye was 6/4. With correction, sphere +1, the vision in the left eye was 6/10.

DISCUSSION

Until Lewis, in 1919, published his report demonstrating the selective affinity for the iris of *Streptococcus viridans* from a focus of infection of a person suffering from iritis, there was little direct evidence to prove that organisms may assume an affinity for the iris without being sensitized by passage through eyes. Irons, Brown, and Nadler injected dead organisms into the anterior chamber of the eye of a rabbit and later injected living organisms into the blood stream of the rabbit. Iritis developed in the previously injected eye and they concluded that the previous injection of the killed organism tended to lower the resistance of the eye, making it more susceptible to attack by this particular strain of bacteria. Thus the iritis simulated recurrent iritis in man. The organism used was obtained from a person who had purulent dacryocystitis. It had not produced lesions in the iris of the patient. It is hardly plausible that its development in the lacrimal sac would raise its affinity for the uveal tissue of the eye because of its juxtaposition, or because of the function of the lacrimal apparatus.

Injection of strains of organisms taken from foci of infection of persons suffering from acute or chronic iritis produced other lesions in the animal, but although large doses were given the rabbit did not develop iritis.

Levy, Steinbugle, and Pease attempted to produce iritis in rabbits by injecting bacteria into the lymph channels, but all their animals died without showing eye lesions, so they decided they would have to use some other animal in their experiments.

During several years of animal experimentation, Rosenow collected

and published notes on forty-eight cases of ocular lesions produced in rabbits by inoculation, but of these only nine had iritis. The sources of the bacteria used in his experiments were varied, but none, so far as we know, were taken from persons who were subject to attacks of iritis. There were no opportunities for the organism used to be sensitized by passing through a host having eye disease, so we may believe that organisms (streptococci) may develop an affinity for the iris without having lived in a host having lesions of the iris.

The frequency with which bacteria from persons having rheumatism attacked the eye led Rosenow to believe that there is a closer connection between iritis and rheumatism than between iritis and other bacterial diseases. This relationship, however, holds more for cases of infectious arthritis and localized muscular rheumatism than for acute rheumatic fever. In man the attacks of iritis produced by focal infection may be of any degree of severity. Mild attacks of iritis may occur, "which amount to no more than a transient hyperemia of the conjunctiva or a slightly troublesome photophobia. A rapid succession of mild attacks extending over a period of several years has been demonstrated to be due to periapical infection."¹

One of our experiments seemed to show that similar attacks of iritis may occur in the animal, and that the organisms isolated from a focus of infection during an acute attack, or an exacerbation of chronic iritis, are more prone to localize in the iris and produce inflammation than those taken from persons who have not suffered from acute attacks of iritis for a number of years. Some of the patients, in these experiments, had had low grade uveitis with punctate keratitis and posterior synechia for years; they had numbers of infected teeth from which streptococci were isolated and cultured and injected into rabbits without noticeable symptoms in the rabbit. It is possible that the iritis of these patients was not due to focal infection around the teeth, even when the organisms usually found to produce iritis were present, or that the organisms were obtained after they had lost their virulence, or that too small doses were given to the rabbits. In some of the animals the muscle and periosteal lesions indicated a virulency of the organisms injected, but the fact that iritis did not develop could not be interpreted as meaning that the iritis in the patient was not caused by this particular strain of bacteria. It was impossible to secure the results desired except by inoculating with fresh cultures (twenty-four hours or less). Again, other organisms were so attenuated that massive doses failed to

produce symptoms in the inoculated animal, even though primary cultures were used. Iritis was produced in the rabbits whenever injected with a culture taken from a person having an acute iritis, but was in no instance produced when inoculated with organisms taken from persons whose eyes were not acutely inflamed.

The symptoms and course of the iritis in the rabbits ran about the same as in the patients. The first sign is hyperemia of the conjunctiva and sclera about the limbus. This is followed by injection of the vessels on the iris, swelling of the iris tissue, discoloration of the iris due to congestion, a slight contraction of the pupil, and turbidity of the fluid of the anterior chamber. The pupil did not contract to less than half its diameter in any case.

That the iritis was produced in the animals by bacteria carried to the eye by the blood stream was amply demonstrated in these experiments. In one case the culture made from the iris of a rabbit was injected directly into the anterior chamber of the right eye of another rabbit (Rabbit 90). The following day the same organisms, green-producing streptococci, were recovered from the uninoculated left eye. Fluid from the anterior chamber of this eye was then injected into the anterior chamber of the left eye of another rabbit (Rabbit 94). After ten days the rabbit was necropsied, and the organism was recovered from the iris of the uninjected right eye, thus showing that the organisms gained access to the blood stream of the injected eye and collected in the other eye. There were hemorrhagic lesions in other parts of the body which also yielded pure cultures of green-producing streptococci. The same organism was also recovered in cultures of the blood of the heart.

The organisms most frequently obtained in the cultures from dental abscesses and granulomas were green-producing streptococci (in short chains and as diplococci, *Streptococcus viridans*) and staphylococci. In watching these experiments we were convinced that the *Streptococcus viridans* was the organism that produced the lesions in rabbits and that the staphylococcus was a harmless organism. The best proof of this assumption came from the culture made of the lesions produced in the animals by the inoculation of the mixed primary culture. In all instances the cultures made of hemorrhagic lesions around the muscles, the periosteum, the jaws, from the anterior chambers of the eyes, and of bits of infected iris tissue produced only *Streptococcus viridans*. Staphylococci were not present.

Plate cultures of the organisms were made at the time the cultures were made in long tubes of liquid medium. On the plates large numbers of colonies of streptococci and a few colonies of staphylococci appeared. Attempts to produce iritis in rabbits with organisms grown on the plates were never successful, since the bacteria grown in this manner soon lose their peculiar infecting power for certain tissues; they retain it, however, when grown in tall tubes of medium. Our experiments sustain Rosenow's contention that in order to retain a specific affinity the organisms must be grown under conditions of oxygen tension similar to those to which they are accustomed. In the tall tube the organisms usually develop near the bottom and gradually come to the top as they acquire the ability to grow in the presence of more oxygen. One reason why other experiments have failed to produce the organisms with selective affinity probably is owing to the fact that the organism responsible for the specific lesion succumbed to the air during the growth of the culture, or lost its affinity through acquiring ability to live under changed environment.

The largest hemorrhages in the iris of the rabbits in which iritis was produced occurred at the juncture of the iris and the ciliary body, where there is a change from highly vascularized tissue to relatively poorly vascularized tissue, with resulting diminution of available oxygen, and in consequence diminished resistance to invading organisms. Similar lesions were found in muscles of the legs, near the tendons, in the periosteum, and around the roots of the teeth. Whether oxygen tension is the chief factor in the selection of the tissue affected cannot be determined from these experiments, but they sustain the conclusion suggested in Rosenow's experiments with streptococci of muscular rheumatism and arthritis.

We may, therefore, conclude that iritis is produced by bacteria arising from foci of infection around the roots of teeth and in the tonsils, that it is an inflammatory reaction brought about by the presence of bacteria in the tissue of the iris carried to the iris by the blood stream from the foci of infection, and that such bacteria have the ability to grow and do grow in such environments. Iritis caused by bacterial infection seems to be an inflammation of muscle tissue at the place corresponding to the parts of muscles effected in rheumatic affections of the limbs and trunk. Organisms have repeatedly been recovered from muscular lesions of the legs and trunk, and when injected into animals produced similar lesions. In numerous instances the muscles and parts

of muscles affected in the animal correspond to the muscles and parts of muscles affected in the host from which the organisms were obtained. That there is a close similarity between the lesions of the leg and the trunk muscles in rheumatism, and the lesion of the iris in iritis, has been demonstrated time and again in the cases here reported. That they may have a common source is suggested by the fact that they can be produced in the rabbit by the same culture at the same time, almost to the total exclusion of other types of lesions or similar types of lesions in other than muscle tissue.

Therefore, we may conclude that iritis of focal infection origin is a myositis caused by an organism that at some period of its growth may cause iritis, and at other periods inflammation of some other muscle. We may further conclude that this affinity for iris tissue becomes a function of the organism spontaneously, or may be acquired by growing on iris tissue, that the affinity for the iris is easily lost by the organism when grown in different environments, and that it will change its affinity for special structural tissue or even lose its virulency to a marked extent.

As the bacteria around the teeth and tonsils are constantly undergoing changes of environment, they suffer a change of function and a change of virulency. There is also a change in the resistance of the body to bacterial invasion, so that in the human body a constant warfare is going on between bacteria and the body tissues and fluids. Iritis occurs as a localized seat of this warfare within the eye and is in all possible respects similar to reactions brought about in other parts of the body by the presence of the same bacteria at different times of the life cycle of the organism.

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RETINITIS OF CARDIOVASCULAR AND RENAL DISEASES*

WILLIAM L. BENEDICT

Some features of the ophthalmoscopic picture of the retinitis of cardiovascular disease and of renal disease are so uniformly found that their presence or absence may be used as a basis for the classification of the retinitis into three fairly distinct types as follows:

1. The retinitis of acute nephritis.
2. The retinitis of chronic hypertension and nephritis.
3. The retinitis of arteriosclerosis.

To these three types must be added one other that may complicate the retinitis of chronic hypertension and nephritis, and the retinitis of arteriosclerosis, being somewhat dependent on arterial changes for its presence, that is, the retinitis of diabetes. It is quite probable that this type does not depend on diabetes alone.

Arteriosclerosis may or may not be a factor in the production of the retinitis of acute nephritis. In severe cases of acute nephritis, especially in young persons, there may not be any sclerosis of the retinal arteries. If the nephritis does not last too long all evidences of retinitis may disappear and the function of the eye be unimpaired. If the nephritis and retinitis should last for a long time, however, or if there should be a number of recurrences of the retinitis, although of mild degree, the retinal arteries will then show signs of degeneration and sclerosis.

Nephritis may occur in a person who has a well developed general or localized arteriosclerosis with fibrosis or sclerosis of the retinal arteries. The ophthalmoscopic picture, then, is composed of features characteristic of arteriosclerosis and of acute or chronic nephritis as well. This is the form most commonly found in cardiovascular-renal diseases of middle aged and old persons, the albuminuric retinitis that is of such grave significance. It may follow arteriosclerosis from any cause, and is usually accompanied by high diastolic blood pressure and increased blood urea with decreased functional activity of the kidney. In young

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persons it may result from repeated attacks of nephritis of mild severity, or a single attack of nephritis in persons whose arteries have become prematurely sclerosed.

The retinitis of arteriosclerosis was described by Moore, in 1916, as a condition separate from the retinitis of nephritis, and my own observations prove conclusively to my mind that there is a distinction. However, the retinitis of arteriosclerosis comes rather late in the course of the disease, and the affections of other organs, particularly of the kidneys as a result of sclerosis of their vessels, often produce retinal changes also, so that the ophthalmoscopic picture is made up of features characteristic of the two diseases, arteriosclerosis and nephritis. If the sclerosis of the retinal arteries is pronounced, the characteristic points of distinction between the sclerosis of involution processes, such as atheroma, and the sclerosis of chronic hypertension may be seen, even though signs of renal impairment are also present to complicate the picture. This distinction between the sclerosis of hypertension and other forms was not made by Moore, but I believe that it is as definitely marked and as easily recognized as the distinction between the retinitis of arteriosclerosis and the retinitis of nephritis.

For the purposes of the clinician finding this difference is very significant, and not finding it deprives him of the privilege of actually seeing what is going on in the body. Arteriosclerosis of the retinal arteries from any cause may lead to arteriosclerotic retinitis. Atherosclerosis most frequently produces retinitis through localized lesions in the artery wall and resultant localized areas of retinal ischemia and degeneration. It may exist alone without renal disturbance to complicate the vascular system. But the uniform sclerosis of hypertension may produce the same picture when renal impairment is long deferred, or well compensated, and no renal break occurs.

If to the retinal arteriosclerosis of either of these types are added the hemorrhages and exudate with sugar in the urine, the picture of the retinitis of diabetes is presented.

It may be said, then, that the most prominent factor in the production of retinitis of diseases of the vascular system and of nephritis is sclerosis of the retinal arteries, to which are added other features characteristic of the etiologic factor of the sclerosis, and a careful analysis of the ophthalmoscopic picture presented may indicate the type of constitutional disorder back of it all, and give important information with regard to its severity and course.

The chief reason for the early differentiation of the retinal changes lies in the possibility of averting serious damage to the kidneys by continued high diastolic blood pressure, which produces arterial thickenings. It has been shown that long continued hypertension produces degeneration of the middle coats of the arteries, that in turn contributes to diseases of the kidneys, brain, and other organs. It has been estimated that 40 per cent of persons with high blood pressure have changes of the retinal arteries that can be discerned with the ophthalmoscope, many of them in the early stage of degeneration, and furthermore, that with proper treatment and dietary control the increased blood pressure may be brought down to within limits of safety before organic changes are produced.

The sclerosis of the retinal vessels varies in appearance as the factors producing the sclerosis differ. The sclerosis of involutional degeneration is not the same as that of the degeneration that follows hyperpiesia, and both forms may differ from the sclerosis brought about by the perivasculitis of syphilis, lead poisoning, and other chronic intoxications. The ophthalmoscopic picture is not always clear and opinions of various observers may differ in cases not well marked, but a sufficient number of them may be differentiated to make the attempt well worth while because of the aid given the clinician in his attempt to determine a patient's condition.

When arteriosclerosis and nephritis occur concurrently, or consecutively, the picture presented by the retina is complicated; but a careful analysis of the retinal changes will allow of deductions with regard to which disease is responsible for the most active changes or will indicate the order of occurrence of the changes. When one disease follows another, as for instance, diabetes following arteriosclerosis, the earlier may be so masked by general symptoms and signs of the latter that it is not detected by general examination. Its effect on the fundus, however, may be traced definitely in most instances.

Arteriosclerosis plays a prominent part in the production of the retinitis of nephritis and of diabetes, besides producing in itself a characteristic retinitis. The arteries of the retina are affected in a manner similar to the arteries of the rest of the body. It is well known that atherosclerosis, the involutional type of arterial degeneration of the cerebral vessels, is frequently accompanied by sclerosis of the retinal vessels. The reversal of this is probably always true. A marked atherosclerosis of the cerebral and retinal vessels may be present with

very little change in the systemic arteries, and not necessarily accompanied by high blood pressure. So, too, a systemic sclerosis may occur with or without high blood pressure in a person free from sclerosis of the cerebral and retinal vessels.

The retinitis of atherosclerosis when uncomplicated is characterized by arteriovenous compression, contracted arteries whose caliber is not materially decreased, pipe-stem sheathing, arterial plaques, beading, increase in the light reflex stripe, and silver wire arteries. There are arterial injection of the nerve head, giving it a brick red color, hemorrhages in the nerve fiber layer, proliferation of new vessels, and extreme tortuosity and increase in the number of the arterial twigs in the region of the macula. Small areas of capillaries are deprived of blood supply, giving rise to ischemia and white spots. Only very rarely is edema present.

These evidences of arteriosclerotic retinitis are not always present at all times and all stages of the process. With this ophthalmoscopic picture and low blood pressure, cerebral arteriosclerosis and an absence of systemic sclerosis would be suspected. With high blood pressure, on the other hand, the presence of systemic sclerosis also would be suspected. The sclerosis of the arteries giving rise to this picture of arteriosclerotic retinitis has its origin in atherosclerosis, or toxic end-arteritis known as secondary arteriosclerosis. Most commonly, however, the atherosclerosis is acting alone and with a comparatively low blood pressure, and when increased blood pressure is added, evidences of nephritis may appear with retinal signs characteristic of a renal break. The arteriosclerosis of the atheromatous type is, as far as we know, a primary disease of the arteries and is not dependent on inflammation of any particular organ, or on toxemias. It is the most frequent type of arteriosclerosis found among the insane, and often results in apoplexy or other central nervous system disturbances.

The arteriosclerosis of hyperpiesia is brought about through effort on the part of the arteries to compensate for the increase in blood pressure and to bring about an adjustment between the force of the heart's action and the peripheral circulation.

Whether increased blood pressure precedes capillary fibrosis or whether the fibrosis precedes the hypertension is an unsettled question. "The relation between arterial disease and kidney disease has been much discussed, some regarding the arterial degeneration as secondary, others as primary. There are two groups of cases, one in which the

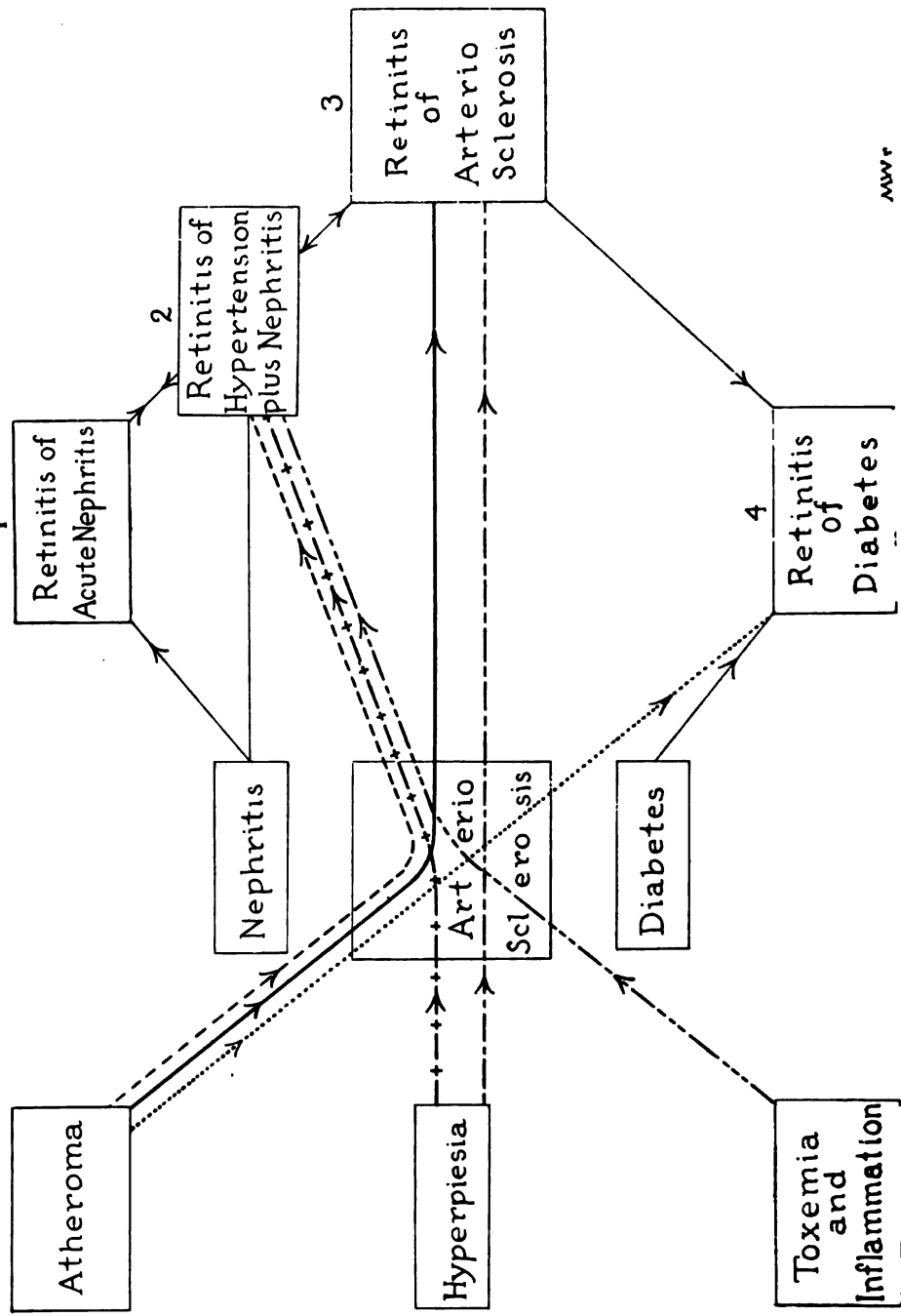
arteriosclerosis is the first change, and the others in which it is the secondary to a primary affection of the kidneys" (Osler).

We may state definitely, however, that fibrosis and sclerosis of the retinal arteries do not precede hypertension, but follow it after an appreciable interval. The hyperpiesia or essential hypertension brings about fibrosis and sclerosis of the retinal arteries, either by intermittent rise of blood pressure over a long period, or by a gradual but steady increase of blood pressure over a shorter period. Under continued hypertension the retinal arteries first become elongated and tortuous, the reflex stripe more prominent, and the arteries appear to be smooth and round. Later, the vessel walls become thickened through a proliferation of the intima and thickening of the middle walls. This thickening leads to subsequent contraction of the arteries, narrowing of the caliber, narrowing of the reflex stripe, arteriovenous compression, increased caliber of the veins, and hemorrhages in the nerve fiber layers and in the deeper layers of the retina. The reduction in the caliber of the vessels is more uniform than in the arteriosclerosis following atheroma. The arteries are not beaded and there is little or no tendency to formation of perivascular sheaths, or to proliferation of new vessels. Quite frequently there is retinal edema. The arteriovenous compression is just as marked as in the arteriosclerotic type of retinitis, but there is not the tendency of the veins to cross under the arteries at right angles. White spots in the retina take the form of small white isolated or confluent plaques, creamy colored layers of exudate giving a rather bright luster. This type of sclerosis is associated with or followed by nephritis. It comes about in the prealbuminuric period (Mahomed), and constitutes the types of retinitis which we recognize as indicative of serious disease. Particularly is this true if, in addition to these features, there is edema over the disc margins with fresh hemorrhage and the formation of cotton-wool exudate. The retinitis of acute nephritis characterized by the intense edema of the nerve and retina, the injection of the smaller vessels, fine hemorrhages, and cloudy exudate, may be added to the retinitis of "hypertension and nephritis," indicating a definite renal break with severe toxemia. Thus it will be seen that on the retinitis of arteriosclerosis which follows atherosclerosis may be superimposed retinitis of acute nephritis. It may be accompanied or followed by hypertension and nephritis, the nephritis of Bright's disease, and the ophthalmologic picture may show the changes characteristic of each.

Clinical Varieties of Retinitis

- 1 = 1
- 2 = 2
- 3 = 3
- 4 = 4
- 5 = 1+2
- 6 = 1+3
- 7 = 2+3
- 8 = 2+4
- 9 = 3+4
- 10 = 1+2+3
- 11 = 1+2+4
- 12 = 1+3+4
- 13 = 2+3+4

(1+4 does not exist)



It is possible for retinitis of nephritis and of hypertension to occur as a result of repeated attacks of nephritis without preceding hypertension, the thickening of the arteries in this case resulting from the repeated perivasculitis and chemical changes in the blood, and the temporary rise of blood pressure during the attack. Combinations of two or more of these three types are quite frequently found in the retinitis of cardiovascular-renal disease.

The retinitis of diabetes, which long has been supposed to be due to some chemical in the blood, is quite probably due primarily to arteriosclerosis. Added to the arteriosclerotic changes are the small, round hemorrhages and retinal exudate and edema which characterize the retinitis of diabetes. Wagener and Wilder, during the past year, have studied cases of the retinitis of diabetes and have found that the characteristic picture known as diabetic retinitis occurred only in persons having arteriosclerosis. It does not occur in the grave forms of diabetes. Diabetes and nephritis may occur together, each presenting characteristic features in the retina. Not infrequently the retinal changes of one disease will be more marked in the retina than the changes of the other disease, and from the picture presented which of the two has been active the greater length of time may be deduced (Fig. 227).

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FIG. 227.—Diagram of the manner in which arteriosclerosis of the retinal arteries may be produced and the most frequent retinal condition following or accompanying such sclerosis.

THE VALUE OF CONSERVATIVE INTRANASAL DRAINAGE FOR CHRONIC EMPYEMA OF THE ANTRUM*

ROY A. BARLOW

The study of 100 cases of chronic empyema of the antrum furnished interesting data with regard to the value of the Krause antrum operation, or window resection. In all the cases studied the infection of the ethmoid or frontal sinuses, which may have existed previously, had cleared up and was not a factor in the infection at the time of the antrum drainage, in other words, the antrum infection was residual, the sinus acting as a reservoir.

In the routine examination of these sinuses it was found that diagnostic puncture is the only reliable means of diagnosis. The roentgen ray was a valuable aid, but not always reliable; the same may be said of transillumination. Many of these patients did not have symptoms referable directly to the antrum, and statements with reference to the possible duration were inaccurate.

TECHNIC

The diagnostic opening was enlarged under the inferior turbinate well toward the floor of the nose. In very few cases was it necessary to sacrifice turbinate tissue.

The after-treatment for the most part consisted of repeated irrigation and suction and simple air-drying. No one particular irrigant was found to be of greater value than another; a mild alkaline solution seemed to be accepted kindly by the tissue. In the air-drying process the cannula is inserted into the antrum and the membranous lining is dried with compressed air without irrigation. This seems to be a valuable procedure in many cases. In some cases in which the condition persisted after irrigation improvement immediately followed the dry treatment. It would appear that the drying of the sinus discourages

* Reprinted from *Minnesota Medicine*, 1921, iv, 445.

further formation of pus. In this connection the word "cured" means that the discharge has cleared up and local symptoms, if any, have subsided. In all probability a chronic sinusitis is never cured permanently; it is a well accepted axiom that once a sinus case, always a sinus case; in other words, the sinus once involved is always liable to flare up with repeated colds or any condition accompanied by a lowered resistance.

Of the 100 cases reviewed, 47 per cent were cured, in the average case in thirty-two days. Seventeen per cent were not improved; 6 per cent were finally operated on radically, either the Caldwell-Lue or Denker operation being performed. Thirty-six per cent were improved, but not cured.

Further analysis demonstrated the fact that in the cases in which the condition did not clear up readily an opening sufficiently large had not been made at the first operation. If the condition did not respond to such treatment it was usually found that definite pathologic changes in the membranous lining, polypoid degeneration, hyperplasia, and so forth, had taken place. A few of the patients who were improved but not cured might have made further progress had they remained longer under treatment. Their condition, however, is reported at the time of their dismissal.

CONCLUSIONS

1. The analysis of these 100 cases demonstrates that intranasal drainage in chronic empyema of the antrum is a safe and efficient procedure in 47 per cent of cases.

2. If adequate drainage and ventilation does not give satisfactory results in from three to four weeks more radical methods should be adopted.

3. Cases in which the membranous lining has undergone hyperplasia or polypoid degeneration will usually need more radical treatment.

4. Dry treatment, or air-drying, seems to be as efficacious as irrigation in many cases.

THE USE OF RADIUM IN THE TREATMENT OF MYXOMATOUS NASAL POLYPS: PRELIMINARY REPORT*

HORACE R. LYONS

My regret to find that the rapidly recurring type of myxomatous nasal polyp does not always respond to medical treatment or surgical measures, led me, about two years ago, to use radium postoperatively.

Notwithstanding personal advice and literature on the subject to the contrary, nasal polyps frequently recur very soon after their removal surgically. The records in our department show that innumerable cases of nasal polyp have not responded favorably to surgical measures even in the hands of competent rhinologists. One reason that the operative results are not always satisfactory is that the polyp has not a definite pedicle attached to the mucous membrane of a turbinate or a sinus. Removal of this tumor and its pedicle and the nearby tissue or cells does not eliminate the condition because the adjacent tissue is also undergoing a myxomatous change, which will soon appear in the form of a polyp. The changed area of mucous membrane around the polyp may extend a considerable distance away from the pedicle. It seems, clinically, that surgery in some instances stimulates the formation of polyps in this adjacent tissue.

The polyp which recurs after the removal of a myxomatous tumor which is attached either to a turbinate or involves the ethmoid cells is also of a myxomatous type and frequently is a larger growth than before the operation.

THE ACTION OF RADIUM

It is well known that radium stimulates the production of fibrous tissue, and this action is utilized in the treatment of myxomatous polyps. After one, two, or three treatments by radium the primary myxoma recurs as a fibromyxoma or a fibro-adenomyxoma. This

* Reprinted from the American Journal of Roentgenology, 1921, viii, 407-408.

type of polyp is very much more satisfactory to deal with than is the myxomatous type.

It must be emphasized, first, that radium inserted, for example, into a large solitary nasal myxoma will not cause such a tumor to disappear nor will it change the type of the tumor; second, radium post-operatively does not prevent the recurrence of a polyp; and third, the use of radium in treating myxomatous polyps associated with a local suppurative process does not cure the latter.

APPLICATION

A hypothetic case illustrating the treatment by and action of radium on myxomatous nasal polyps is as follows: A patient presents himself because of constant nasal obstruction. He gives a history of having consulted a rhinologist four years before, who operated on his nose, removing large masses of jelly-like polyps. He was greatly relieved for a short time, but the obstruction returned and operation for large masses of polyps was again necessary six months after the diagnosis was first made. He has had a total of seven operations for nasal polyps.

Examination reveals a large mass of multiple polyps in the right middle meatus. The polyps are jelly-like and very soft; they appear "water-logged." A specimen is sent to the pathologist, who reports myxomatous polyp tissue. The patient is advised that one or more operations are necessary, and that radium treatments will be used.

A radical operation for the removal of the polyps is performed and all the polyps are removed with a considerable amount of the adjacent tissue which is not frankly myxomatous, but which, as experience has taught, rapidly recurs as such. As soon as the reaction diminishes, from three to six days postoperatively, radium treatment is given and the patient is kept under observation. Soon some very pale tissue in the middle meatus, not quite healthy in appearance, is noted. Within the next week or two this tissue becomes frankly polypous. Local treatment is continued. In case of recurrence in the remaining tissue a section is sent to the pathologist who reports fibromyxomatous tissue. A second operation, not so extensive as the first, is performed. The fibromyxomatous tumor which resembles a fibroma malle is removed surgically much more satisfactorily than the primary tumor. If the recurrence is extensive the second operation is followed in from three

to six days by a second radium treatment; a third treatment is rarely found to be necessary.

DOSAGE

In my early cases I used a 25 mg. tube of radium, screened with a silver tube covered by a sterile rubber finger cot for one hour. Experience gradually eliminated my fear of a burn and indicated that larger doses were necessary. I now use a 50 mg. tube for two hours. Subsequent treatments are given with an interval of one week. The radium tube is put in the region of the myxomatous tissue and made secure by packing with sterile vaselin gauze. The string tied to the radium tube is attached to the cheek by a piece of adhesive tape. After two hours the pack and radium are removed. The reaction resulting from this treatment is not apparent for forty-eight hours or more. In fourteen cases treated with 25 or 50 mg. for two hours no burns occurred.

Conclusions regarding postoperative radium treatment await the test of more time and more experience. I believe, however, that in the stubborn cases of myxomatous nasal polyps, especially those recurring after operative measures, the treatment will result in a change from a myxomatous type to a fibromyxomatous type in which operation may be more successfully performed. Also the polyps recur less rapidly with radium treatment and thus the interval of relief is lengthened.

The detailed report of fourteen cases treated postoperatively since November 1, 1918 will be submitted later.

TWO UNUSUAL NASOPHARYNGEAL TUMORS*

GORDON B. NEW

Unless the nasopharynx is examined routinely in all patients with complaints around the head and neck, many interesting and important observations may be overlooked. I have emphasized this point in a previous paper, an analysis of forty-six nasopharyngeal tumors.¹ Recently I have examined two nasopharyngeal tumors of special interest, one actinomycosis of the nasopharynx; an exceedingly rare condition, and one primary lymphosarcoma of the nasopharynx without symptoms in any way referable to the head. This was found in the course of a routine examination.

ACTINOMYCOSIS OF THE NASOPHARYNX

Case 1 (A35993). Mr. A. E. A., aged forty-five years, a farmer, came to the Clinic January 31, 1921, because of difficulty in opening his mouth and pain in the left ear and upper jaw. He had first noticed this one month before. The pain radiated around the left eye and into the left ear and mastoid region. There was a slight decrease in hearing in the left ear. Three teeth had been extracted without relief from the pain or the ankylosis of the jaw. He had been given morphin for two weeks.

A mass, not ulcerated, was found in the vault of the nasopharynx on the left side; it almost protruded to the midline. It was impossible to see the eustachian tube. The left tonsil on this side was slightly enlarged; the nose and throat findings were otherwise negative. The patient could separate his teeth less than 1 cm. The left ear drum was slightly retracted. There was no external swelling around the head. The eye and neurologic examinations were negative. The Wassermann reaction was negative. It was questionable whether the mass was inflammatory or malignant. The patient and his physician were told that it would not be advisable to remove tissue for diagnosis as the treatment would not be surgical in either case. Radium treatment into the nasopharynx and outside the temporal region was given. Seven weeks afterward the patient returned to the Clinic, a phlegmon having ruptured in the left temporal region just above the zygoma from which actinomycetes were demonstrated grossly and microscopically. The pocket was drained thoroughly, swabbed with iodine, and packed wide open. Potassium iodide was given internally and radium treatment continued.

Four months after the first examination the wound in the left cheek had almost entirely healed, the nasopharynx was negative, the jaw opened normally, and no further pockets had formed. The patient's general condition was much improved and he had no pain.

* Presented at the staff meeting of surgical specialists, Worrell Hospital, Rochester Minnesota, June, 1921. Reprinted from the *Laryngoscope*, 1922, xxxii, 99-102.

COMMENT

This is the first time I have observed actinomycosis involving the nasopharynx and causing a tumor which might readily have been mistaken for a malignant growth. The most common location around the head and neck for actinomycosis is usually in the submaxillary and cervical regions, and many of these cases are taken for simple phlegmons, the result of tonsillitis or infected teeth.



FIG. 228 (Case A25993).—Patient with nasopharyngeal actinomycosis which ruptured externally on the cheek. There was no external swelling at the first examination when the nasopharyngeal mass was present.



FIG. 229 (Case A294938).—Patient with primary lymphosarcoma of the nasopharynx which did not cause symptoms. The tumor was found on routine examination.

Just how the infection reached the nasopharynx in this case is questionable. The patient was a farmer, and had taken care of cattle with this disease. The infection may have gained access to the nasopharynx by direct extension along the inner surface of the ascending ramus of the jaw from the tonsils or teeth, the nasopharynx becoming involved secondarily. No other lesion was visible at the time of the first examination and the history does not aid in determining the source of the infection. The severe pain, and the huge, hard tumor in the

nasopharynx would usually justify the diagnosis of malignancy; fortunately a guarded opinion was given. After thorough drainage of the temporal region the pain entirely disappeared and the general condition improved. The patient is taking potassium iodid up to 200 grains three times a day. Radium is being applied over the temporal region, neck, and into the nasopharynx. The prognosis, of course, is questionable on account of the location of the disease and the possibility of meningeal involvement.

PRIMARY LYMPHOSARCOMA OF THE NASOPHARYNX

Case 2 (A294938). Mrs. T. O. N., came to the Clinic October 29, 1919, complaining of a small area on the left tip of the nose which was causing a burning sensation. Small

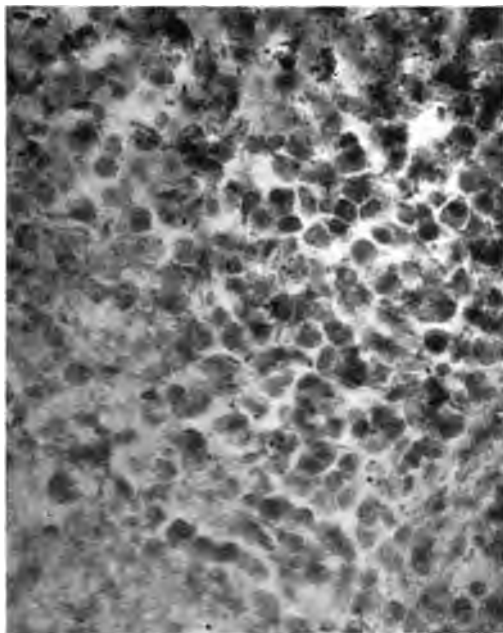


FIG. 230 (Case A294938).—Photomicrograph of nasopharyngeal lymphosarcoma.

scales had been forming on the left tip of the nose and she was worrying about the condition being a cancer. She had no other complaint in her nose, throat, or head. Her general health was good.

Examination of the outside of the nose showed a very small area of keratosis on the left tip. In the right vault of the nasopharynx, in and above Rosenmuller's fossa, a tumor about 2 cm. in diameter was found. There was no definite ulceration. The tissue removed from the tumor for microscopic diagnosis was lymphosarcoma. There were no

glands palpable in the neck. The eye and ear examinations were negative. The hemoglobin was 78 per cent, the erythrocytes 4,054,000, and the leukocytes 12,500, two hundred cells were counted, the polynuclear neutrophils were 75.0, the small lymphocytes 16.5, the large lymphocytes 6.5, the eosinophils 1.5, and the basophils 0.5. The Wassermann reaction and the urinalysis were negative. A diagnosis was made of primary lymphosarcoma of the right nasopharynx.

COMMENT

Primary lymphosarcoma in the nasopharynx without symptoms is a very unusual condition. I have seen similar cases in which the glands of the neck were involved, and in which the primary growth in the nasopharynx was without symptoms. This, however, is the first case I have seen in which there were no symptoms or signs of disease and the routine nasopharyngeal examination was the only way in which the tumor could be found. Radium treatment in a case of this type is very satisfactory and may permanently clear up the trouble.

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MELANO-EPITHELIOMA OF THE PALATE*

GORDON B. NEW AND FRENCH K. HANSEL

In a thorough review of the literature we have been able to collect only twenty-four cases of primary melano-epithelioma of the palate. One case at the Mayo Clinic, which was observed in 163 cases of melano-epithelioma of the body in general, and thirty-two primary epitheliomas of the palate, makes a total of twenty-five cases.

The first melano-epithelioma of the palate was reported by Weber in 1859. The twenty-four cases were reported by Weber, Ried, Albert, Gussenbauer, Treves, Maude, Volkmann, Martens, Broekaert, Liebold, Fuchs, Stein, Eve, Ball, Seidel, Mayer, Roy, Eisenmenger, von Mikulicz, Braun, Billroth and Eder, who each reported one case, and Ebermann, who reported two cases. All of the cases were verified with the exception of those reported by Billroth, von Mikulicz, Braun, and Eder. These were cited by Seidel, who did not give the references to the original articles.

Melanotic tumors have been variously classified as melano-epithelioma, melanosarcoma, melanocarcinoma, melanoblastoma, melanoma, and chromatophoroma. Broders and MacCarty prefer the term melano-epithelioma whether the tumor occurs in the mucous membrane or in the skin, since they believe that the pigment-bearing cells arise directly as a proliferation of the germinative cells of the skin or the cells of the parenchyma of organs.

Symmers believes that the term chromatophoroma or melanoma should be used, since the lesion arises from a pigment-bearing cell known as the chromatophore.

ETIOLOGY

Melano-epithelioma, particularly the type originating in the skin, eye, eyelid, mucocutaneous surfaces of the vulva and anus, penis, ovary, epididymis, and pineal gland, arises in pigment-bearing cells. In

* Reprinted from the *Journal of the American Medical Association*, 1921, lxxvii, 19-22.

horses melano-epithelioma is quite common in the anorectal region, where there is an abundance of pigmentary tissue. Leibold has suggested that since the palatal tissue is embryologically derived from the ectoderm, and since this tissue may therefore contain pigment, it may be possible that melano-epithelioma of the palate originates in these cells. The mucous membrane of the human palate is normally nonpigmented, but some animals have a nonpigmented palate; others may normally have dark palates, such as the horse, cow, dog, deer, and fox. The maki, on the other hand, has a pigmented palate. White and dark palates may occur in the same race of animals.

Melanosis of the palate in man may be a precursory sign of future disease, the beginning of a new growth, or a complication of an already existing growth. In only six of the twenty-five cases of melano-epithelioma of the palate were areas of pigmentation noticed previous to the appearance of the growth. In Roy's case the patient had noticed the appearance of a small area of pigmentation following an injury to the palate by a pipe-stem; from this area the tumor developed. In the four cases reported by Ball, Mayer, Eve, and Maude a small area of pigmentation was noticed on the palate previous to the appearance of the tumor. Treve's patient noted an area of pigmentation following an injury to the palate by a dental plate, which he had worn for several years.

SYMPTOMATOLOGY

Practically all of the patients complained only of the presence of a tumor of the palate and sought examination because of it. The tumors did not cause pain unless they were very large, and there was dysphagia and swelling of the mouth and throat. Difficulty in speaking and chewing was complained of in the cases in which the tumor was extensive. Hemorrhage sometimes occurred because of the vascularity of the tumors and their proneness to injury during the process of eating.

In fourteen patients the cervical glands were involved at the time of the first examination. One patient noticed glandular enlargement before the discovery of the primary tumor on the palate.

The duration of symptoms varied from one month to four and one-half years. The average duration was fifteen months. Seven of the patients were women and eighteen were men. The youngest was twenty-four years and the oldest eighty-four, the average age was fifty-four.

HISTOPATHOLOGY

Petit made a series of sections from melano-epitheliomas in animals and described the mechanism of the formation of pigment. The sections were made of different areas of the tumor, such as the nonpigmented, the partly pigmented, and the deeply pigmented, in order to show the formation of pigment in the various stages. It was demonstrated that the melanotic infiltration is produced as a secretion or protoplasmic elaboration of the cell independent of any vascular action. The granules of pigment occur in the cell as the specific granules that are precipitated or concentered in a glandular cell, just as fat granules accumulate in a connective tissue cell in the formation of adipose tissue, with the difference that the fat forms from one to several large droplets, whereas the melanin remains dispersed in the form of granules. Soon after the pigmentation appears the cell, which is fusiform at first, soon becomes globular and so black that the nucleus is invisible. The pigment is first seen in the cell as small dark granules in the protoplasm; as the process progresses the cell gradually becomes darker, finally the nucleus and cell outline become indistinct and a small ball of pigment remains. These balls disintegrate and the tumor becomes a blackish mass. Through the destruction of the vessels in the foci of softening the pigment enters into the blood stream which carries it over the body, and causes a generalized pigmentation. Likewise emboli of living cells may form in a vein and lead to metastasis.

Microscopically these tumors show an alveolar arrangement of spindle and oval cells and occasionally giant cells. Some of the cells are pigmented and some are not. The former show varying amounts of brown and black pigment. When the cell becomes filled with the pigment the nucleus and cell outline are indistinct and only a small dark mass can be seen. Fibrillar connective tissue also shows the presence of pigment granules. Areas of degeneration and hemorrhage are seen in various places in the tumor. The endothelium of the blood-vessels may also contain pigment granules. Dipping down from the surface epithelium areas of epithelial hyperplasia may be traced into the main portion of the growth. Early recurrences may not show pigment.

A tumor which is only slightly pigmented may give rise to a very deeply pigmented metastasis, and conversely a deeply pigmented primary tumor may metastasize in the form of a nonpigmented or only slightly pigmented tumor.

Melano-epithelioma of the palate metastasizes early, usually first in the neighboring lymph glands, and late as a general metastasis. Melano-epitheliomas of the eye and skin, on the other hand, may metastasize very early in the lungs, liver, brain, skin, and so forth.

DIAGNOSIS

The diagnosis of primary melano-epithelioma of the palate usually is not difficult. The rapidly growing, pigmented, nodular, somewhat pedunculated tumor, usually soft in consistency and vascular, is characteristic of this type of neoplasm. The glands of the neck become involved early by metastasis and later a general melano-epitheliomatosis may occur. An early melano-epithelioma of the palate may be confused with other forms of pigmentation such as that following small hemorrhagic areas in the submucosa in certain blood dyscrasias. Poisoning with bismuth and lead may also cause a pigmentation of the gums and palate. The following case is an illustration of a mistaken diagnosis of melano-epithelioma of the palate:

Case A271870. A woman aged forty years, came to the Clinic with a small pigmented nodule of the palate which had been diagnosed elsewhere as melano-epithelioma. Two months before she had noticed the growth while she was inspecting her teeth. She consulted her family physician, who suspected melano-epithelioma, and advised her to look elsewhere on her body for evidence of pigmentation or primary growths. Three small areas of bluish discoloration were found on the vulva. There was no history of injury to the palate, but when she was five years of age she had fallen over a chair and injured the vulva. Several other physicians corroborated the diagnosis of the first consultant, and gave the usual poor prognosis.

Our examination of the palate revealed a small, slightly elevated blackish, hard nodule about 5 mm. in diameter in the right side of the soft palate, near its juncture with the hard palate. A general examination did not reveal evidence of other pigmentation of the skin. Three small hemangiomas on the vulva were found.

The patient was advised to have the nodule of the palate widely excised for diagnosis. Encysted in the removed tissue was a small piece of lead 4 mm. long from a lead pencil. Microscopic examination of the tissue did not show malignancy. The lead had become diffused in the tissues and caused a black pigmentation characteristic of melano-epithelioma.

PROGNOSIS AND TREATMENT

Rapidly growing melano-epitheliomas are considered the most malignant type of neoplasm. There are, however, other types that are slow growing and are less malignant, for example, the malignant moles. In seventy cases of melano-epithelioma of the skin, reported by Broders, the average duration of the lesion before examination was eleven years.

Thirty-eight of these patients were traced following operation. Twenty-four (63 per cent) died within one year following the last operation; the average duration of life was eleven months and three days.

Seventeen of the twenty-five patients with melano-epithelioma of the palate were operated on, the remaining eight were considered inoperable. Several types of operation were employed, such as resection of the upper jaws and palate, wide excision of the growth by means of the chisel and mallet, curettement, and the cautery. In our case the growth was cauterized with soldering irons and radium applied. We do not believe that removal of the glands of the neck in an attempt to block the growth from metastasizing is of value nor is a block dissection of value when a gland of the neck is involved.

Since many of the twenty-five cases were reported shortly after operation, it is not, of course, possible to give a prognosis with regard to end-results. It is evident, however, that surgical intervention or radium either locally or over the neck are usually futile.

REPORT OF A CASE

Case A298143. X. D., a farmer, aged sixty-two years, came to the Clinic November 28, 1919, because of a tumor about 1 cm. in diameter on the right side of the palate which he had noticed one month before by feeling it with his tongue. The tumor had grown very rapidly for the last two weeks. A piece of the growth was removed by the patient's home physician and microscopic examination revealed melanosarcoma. The patient had not worn dental plates and there was no history of trauma or pigmentation on the palate. The tumor had bled slightly on several occasions. A slight defect in the speech was the only symptom manifest.

Examination revealed a tumor on the right side of the palate about 3 by 4 cm., extending from the posterior margin of the hard palate half-way forward on the palate. At the right posterior lateral margin it extended down on to the anterior pillar. The growth was pedunculated, irregular, with a nodular surface, but was not ulcerated. It was soft, mottled with bluish green, pink, and black areas, and was very vascular, bleeding easily on manipulation (Figs. 231 and 232). The pedicle was attached to the posterior margin of the hard palate. There were no enlarged glands and no evidence of pigmentation or metastasis elsewhere. Roentgenogram of the chest was negative. Examination of the urine was negative for melanin and the Wassermann reaction and the eye findings were negative. A clinical diagnosis of primary melano-epithelioma of the palate was made. The unfavorable prognosis was explained to the patient, but it was decided to attempt the removal of the growth.

December 3, 1919. A piece of the growth was removed for microscopic examination; this showed the typical structure of melano-epithelioma. The tumor was thoroughly cauterized with soldering irons, and twelve days later 50 mg. of radium was applied to the open wound for ten hours with no screening except the radium container, less than 1 mm. in thickness.

January 20, 1920, the patient returned with the wound of the palate healed and no

evidence of recurrence or metastasis. A slightly enlarged hard gland was palpable in the right submaxillary region. Four thousand mg. hours of radium were applied to the right submaxillary and cervical regions with one inch distance and 2 mm. of lead screening. The patient was examined again March 15, 1920. There was no local recurrence nor change in the glands, and no general metastasis. Roentgen-ray treatment was given to the right side of the neck.

The patient continued to receive occasional roentgen-ray treatments over his neck, and November 29, 1920 he returned with a recurring growth on the palate 1 by 2 cm. A small portion of the growth was covered with mucous membrane and the remaining



FIG. 231.—Melano-epithelioma of the right palate and anterior pillar.

part was pedunculated. In the right submaxillary region was a large, hard, freely movable gland about 4 cm. in diameter, and in the right upper deep cervical region a hard slightly fixed gland about 3 cm. in diameter. Roentgen-ray treatment was applied to the glands.

February 8, 1921, the growth had increased to 2.5 by 0.5 cm., and involved the right side of the palate at the juncture of the hard and soft parts, extending from the alveolar process to the midline of the palate. The growth was soft, vascular, and fixed to the underlying bone. It was pigmented except for a small area near the middle. The gland in the right submaxillary region had increased to 4.5 cm., and the one in the upper

deep cervical region to 5 cm. in diameter. No other glands were found to be involved and there was no evidence of general metastasis. The general health of the patient was

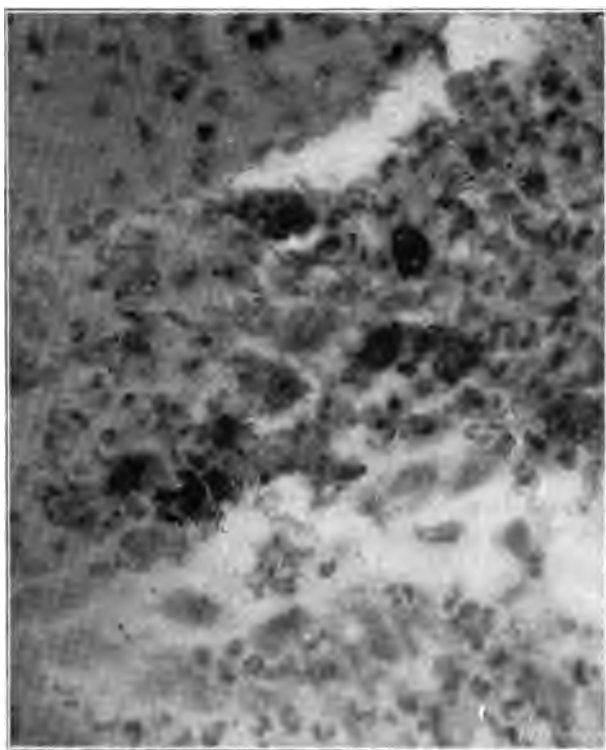


FIG. 232.—Photomicrograph of melano-epithelioma of the palate.

good. Roentgen-ray treatment was applied to the glands. The patient has not been examined since, but the prognosis is very unfavorable.

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TREATMENT OF MULTIPLE PAPILLOMAS OF THE LARYNX IN CHILDREN*

GORDON B. NEW

The treatment of multiple papillomas of the larynx in children has always been difficult because of the tendency to recurrence. Many methods have been employed, such as tracheotomy, thyrotomy and cauter, endoscopic operative measures, fulguration, the application of various medicines locally, and roentgen ray and radium. The lack of uniformity of methods employed in the treatment of this condition emphasizes the fact that the results have not always been good. During the last six years I have treated the condition by radium inside the larynx and outside of the neck, and the results have been much more satisfactory than with any previous methods.

In 1901, McKenzie established the fact that in many cases multiple papillomas of the larynx in children disappear of themselves if a tracheotomy is performed; he advocated tracheotomy instead of treating the papillomas. Clark, in 1905, and Smith, 1914, stated that they believe tracheotomy to be the most efficient method of treating these cases. While the value of tracheotomy is well known, cases are reported in which the patients have worn tubes for years without any improvement of the condition. I examined a woman, aged twenty-two years, who had worn a tracheotomy tube since she was two years, and her larynx was filled with papillomas. Polyák, in 1911, discussed the treatment of three patients by radium, two adults and one child. He believes that radium will take the place of operative measures in these cases. Abbe, in 1898, was the first in this country to treat multiple papillomas of the larynx with radium. The patient was a woman aged thirty years. In 1912 he treated a girl aged sixteen years with papillomas of the larynx, with complete clearing up of the condition. Harris, in 1913 and 1914, reported thirteen collected cases which included Abbe's, Polyák's, and Freudenthal's cases. Cohen told of a child aged five years, treated by Bernham, in whom the results were

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exceedingly good. Plum, in 1920, reported sixteen cases of multiple papillomas; four of the patients were treated by radium, two with good results, and one with a fair result. Plum believes that the results are encouraging. Several observers report poor results by the use of radium. Hopkins, in 1914, reported a case in which radium was used, and was followed by adhesions of the anterior three-fourths of the larynx, and brought up the question of whether or not the scarring was due to the radium treatment. Iglauer, in discussing Smith's article, spoke of the scarring in the larynx following the treatment by 50 mm. radium for seven or eight hours. Jones reported a case of multiple papillomas unsuccessfully treated with radium, but the dosage was not given. Duffey, in 1919, reported a case of a child, aged three years, who developed diffuse thyroiditis and died, following the application of radium inside and outside the larynx. Lynch has perfected the suspension apparatus that is now used and which has added a great deal to the efficient care of these patients. His results in removing the papillomas by operative measures have been superior to any others on record in this country. He, however, now believes that the dissection of multiple papillomas from the larynx is an unsuccessful procedure and that the best method for treating these conditions is by fulguration or by acid nitrate of mercury.

During the years from 1914 to 1920, I have examined at the Mayo Clinic twenty-six children under twelve years with multiple papillomas of the larynx. The youngest was ten months, and the oldest was twelve years. Such patients are usually brought to the Clinic because of hoarseness and shortness of breath, which may have started at the age of two or three months, as a slight wheezing or crowing cough, or the condition may not have been noticed until the child began to talk. Sometimes the first symptoms are not observed until the child is three or four years of age. He may later become unable to speak above a whisper, and may get blue when crying and require emergency tracheotomy. Frequently parents state that the hoarseness came on after whooping-cough, measles, or a cold, which they believe is the cause of the trouble.

Multiple papillomas of the larynx are often diagnosed as laryngismus stridulus, asthma, and enlarged thymus, but these conditions are readily ruled out by careful history taking. The diagnosis can be made only by laryngoscopic examination, by means of which the typical picture is seen.

Many of the patients in my series had been operated on by endoscopic methods. One patient had had six thyrotomies and cauteries performed by a general surgeon and was wearing a tracheotomy tube. The glottis was so badly scarred that a small probe only could be passed through it. One patient had had six suspensions and the removal of the papillomas, but when he came to the Clinic a large papillomatous mass stood up from the larynx and almost filled the laryngopharynx.



FIG. 233.—Specimen taken at necropsy of a multiple papilloma of the larynx in a child who died on the train on the way to Rochester for an examination.

The upper margin of the mass was on a level with the tip of the uvula. The conditions of the other patients were not unusual; the larynx was usually filled with a varying amount of papillomatous tissue. Nineteen of the patients had had tracheotomies previously or tracheotomy was performed for marked dyspnea shortly after their arrival. Tracheotomy was not performed unless obstruction made it necessary. One patient not included in the group of twenty-six died on the train coming to Rochester from laryngeal obstruction (Fig. 233).

TREATMENT

The treatment in this series of cases was given under ether, by means of a Lynch suspension apparatus. Except in a few of the early cases no attempt was made to remove the papillomas. A small tube, containing the emanations or the radium salt, was inserted into the glottis and held there by means of forceps. The tube was kept moving under direct observation so that no particular area was overtreated and so that the part needing treatment received it (Fig. 234). The patient was kept asleep during the entire treatment, and from 75 to 150 mg.,



FIG. 234.—A child under suspension. The forceps in the mouth is shown holding a tube of radium directly in the glottis. The radium tube is kept moving during the application.

or millicuries of radium, were used for from twenty to thirty-five minutes, and occasionally longer if indicated by the particular condition. No screening was used except the silver tube which contained the salt, or the emanation, and is less than 1 mm. thick. Patients were treated, as a rule, about once in six weeks or two months. If recurrence was noted further treatment was given before the recurrence became marked. Parents are always told that unless the child can be brought back at definite intervals it is of little use to begin treatment. The most suspensions given in one case were six, and the least one. Besides these suspension treatments, radium was applied

outside the larynx; as a rule about 3,000 mg. hours were given, using 2.5 cm. of wood and 2 mm. of lead screening. These external applications were frequently given between the suspension treatments.

RESULTS

Of the twenty-six cases, nine cannot be considered in the results. One patient died about twelve hours after an emergency tracheotomy. One patient died at home between treatments for the want of a tracheotomy, after having had dyspnea for a week. Four patients did not remain for treatment, since they could not return at definite intervals. Two patients received one or two treatments and were unable to return. One patient could not be traced, but at the last examination was remarkably improved.

Of the seventeen patients of whom definite information was obtained, eleven are entirely free from papillomas; nine of these had had tracheotomies and the tracheotomy tube had been removed. The tube is always left in place at least six months after the larynx is free from papillomas. One child, on whom a tracheotomy was performed at the age of two and one-half years, had worn the tube for one year and seven months and it could not be removed after the larynx was entirely free from papillomas because of the apparent collapse of the trachea above the tracheotomy opening. A two-way tube was inserted in place of the old tube, and later this was removed, and the tracheal opening closed. This was the only instance in which any difficulty occurred in removing the tracheotomy tube. Two of the eleven patients did not have tracheotomies and were not suspended; they received treatment entirely outside the larynx because they had colds at the time of their examinations and it was thought inadvisable to give ether. Six of the seventeen patients are still under treatment, but five during the last year only. The larynx of four of the six patients is almost entirely cleared up; possibly there may be an occasional papilloma, but the voice is fairly good. Three of these four had tracheotomies and they can cork their tracheotomy tubes. One of the six is much improved, but papillomas are present and the voice is hoarse. This patient is wearing a tracheotomy tube and can cork it. One of the six patients, the one referred to as having had so much operative work before coming to the Clinic, is so remarkably improved that the papillomatous mass is now intralaryngeal. In the entire group I have not seen any bad results follow the use of radium, but I believe that this is undoubtedly owing

to the fact that the radium was under direct observation and was kept moving while in the glottis (Fig. 235).



FIG. 235.—An extensive papilloma of the larynx which has extended up into the pharynx from the glottis, the result of repeated operative treatment. The condition has now almost entirely disappeared under radium treatment.

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CICATRICAL LARYNGOPHARYNGEAL DIA- PHRAGM*

GORDON B. NEW AND PORTER P. VINSON

Pharyngeal strictures are of three types: (1) The nasopharynx closed off from the pharynx and mouth by adhesions from the soft palate to the posterior pharyngeal wall; (2) the soft palate scarred down to the base of the tongue, leaving a small opening laterally for respiration and the passage of air, a much smaller group, and (3) a cicatricial diaphragm in the laryngopharynx which joins the base of the tongue at about the level of the epiglottis to the posterior pharyngeal wall; there is a very small opening for the passage of food and for respiration. The cases in Group 3 are practically all syphilitic in origin, although Fleischmann and Borchard have advanced the possibility that they may sometimes be due to diphtheria, lupus, or other nonsyphilitic ulcers. They report a case of a boy aged sixteen years who had a nasopharyngeal and laryngopharyngeal stricture following diphtheria. There were no signs of congenital or acquired syphilis in the patient or his parents, and as the scars were not typical of syphilis it was concluded that the stricture might be postdiphtheric. In the case reported herewith the cicatricial pharyngeal diaphragm of the laryngopharynx with strictures of the esophagus was caused by swallowing lye. In our review of the literature we were unable to find a similar condition caused by swallowing caustics.

REPORT OF CASE

Case A293223. Mr. P. N., aged twenty-eight years, came to the Clinic October 17, 1919, complaining of inability to swallow or to breathe through the pharynx; he was wearing a tracheotomy tube and a gastrostomy tube. He asserted that he had been perfectly well until the night of October 6, 1917, at which time while walking in his sleep he drank a solution of lye. He woke up immediately and believed that he had been able to empty most of the solution out of his mouth without swallowing. A physician was called, who gave olive oil and lard in milk. The tongue and mouth swelled and for twenty-four hours he could not eat or drink; the following day, however, he was able to eat soft foods. His mouth and throat were quite sore for five or six weeks, but he was confined to bed for only four or five days. Within ten days he began having trouble swallowing

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solid food, but he swallowed fluids very well and had no difficulty in breathing. November 15, 1917, following instrumentation in an attempt to dilate the esophagus he had a marked

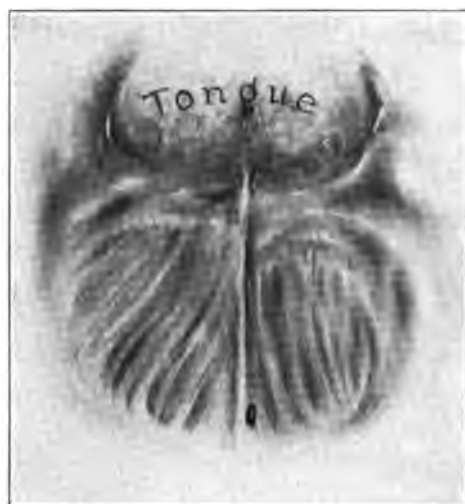


FIG. 236.—Cicatricial diaphragm of the laryngopharynx as seen by suspension laryngoscopy.



FIG. 237.—Postoperative appearance.

subcutaneous hemorrhage into the tissues of his neck, increasing its circumference to 51.25 cm. three hours after treatment. The esophagus closed completely and he began to have difficulty in breathing, which became progressively worse. The patient was fed

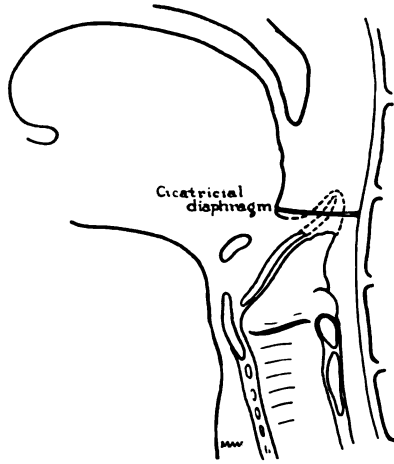


FIG. 238.—Diagram showing location of cicatricial diaphragm of laryngopharynx.



FIG. 239.—Tracheotomy, gastrostomy, and empyema tubes in place.

by bowel and lost weight from 138 to 75 pounds. December 17, 1917, a tracheotomy and a gastrostomy were performed. At first the food was put directly into the stomach

through the gastrostomy tube and the patient improved very little. Very soon he found that by chewing the food and then putting it into his stomach through the tube his nutrition improved and he gained in weight. He stated that he had been working for the last two years as instructor of manual training in a high school.

When examined the patient weighed 124 pounds. He wore a tracheotomy tube and a gastrostomy tube. Examination of his mouth and posterior pharyngeal wall did not reveal scars of any kind. By means of a laryngeal mirror a scarred diaphragm was found joining the base of the tongue around the region of the epiglottis to the posterior pharyngeal wall; there was a small opening just to the right of the middle line, close to the posterior pharyngeal wall, which admitted a very small probe. By closing the tracheotomy opening and exhaling, a few bubbles of air could be forced through the opening. The



FIG. 240.—Patient at time of dismissal.

patient stated that milk taken into the stomach through the gastrostomy tube sometimes regurgitated into the mouth through the opening. The diaphragm was quite thin; a bent probe could be passed in all directions from the small opening. His general examination was negative.

October 28, 1919, by means of laryngeal suspension under ether a further examination was made (Figs. 236, 237, and 238) and a circular piece was removed from the diaphragm with a knife. There was practically no bleeding on account of the thinness of the scar. The opening into the larynx and esophagus could be seen quite readily. The following morning the patient was able to eat oatmeal, the first food he had eaten since the gastrostomy, and he could cork the tracheotomy tube. During the next few days the opening showed a tendency to close, and the patient swallowed a silk thread which was drawn out

through the gastrostomy tube. The patient was getting along so well with his nourishment that he did not wish to have anything further done. However, a sound was passed into the esophagus with the thread as a guide and a stricture was located 20 cm. from the incisor teeth. On passing dilating olives, a second stricture was located just below the first. After the first dilatation, which was carried to 29 French, the patient was able to take any type of food, and by repeated dilatations the lumen of the esophagus was gradually brought to 37 French. With the first two or three dilatations rather profuse bleeding occurred, but with further treatments the bleeding stopped.

January 15, 1920, the patient developed influenza, followed by bronchopneumonia and a right empyema. This effusion was aspirated several times, and finally it was necessary to make a stab wound in the chest and insert a tube for permanent drainage (Fig. 239). Although at this time the patient was able to take food, it was thought best to leave the gastrostomy tube in place, since his illness was quite severe, and esophageal dilatations were postponed. As he convalesced from the empyema the tracheotomy tube was removed, then the gastrostomy tube, and finally the empyema cleared up completely (Fig. 240).

The patient was dismissed from our care July 23, 1920, feeling perfectly well. The pharyngeal opening was about 1.8 cm. in diameter.

The patient is treating the pharyngeal stricture by dilating it with his index finger; the esophageal strictures are being dilated from time to time by sounds, using a previously swallowed silk thread as a guide.

COMMENT

Most authors believe that in the treatment of laryngopharyngeal cicatricial diaphragms dilatations and small cuts into the scarred opening in different directions give the most satisfactory results. Axhausen has treated two cases by means of a pharyngotomy and plastic operation, in order to replace the scar tissue in the pharynx. He reports very satisfactory results from this treatment, and believes that it is better than the continuous dilatation which is necessary to prevent a recurrence of the stricture.

The interesting points in our case are that (1) the laryngopharyngeal stricture was the result of swallowing lye, (2) that the patient earned his living for two years while he wore a tracheotomy tube and a gastrostomy tube, feeding himself by means of chewing food and spitting it into the gastrostomy tube funnel, and (3) at one time he carried three tubes, tracheotomy, gastrostomy, and empyema, and ultimately was able to get along without any of them and is now following his vocation.

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THE ROENTGENOLOGIC ASPECT OF PULMONARY METASTASIS*

RUSSELL D. CARMAN

In 1916, Moore and I published a paper concerning pulmonary metastatic malignancy based on the study of seventy-one cases. Since then our material has been increased by 196 additional cases, and I have reviewed these in order to determine whether the amplified statistics sustain our original conclusions and whether any additional facts of interest could be elicited.

Without going into tiresome details it may be said that the enlarged series tends to confirm our former conclusions, that (1) pulmonary metastatic malignancy may occur regardless of the seat of the primary focus, (2) it bears no relationship to the extent or duration of the primary disease, (3) it can be discovered in many instances only by the roentgen examination, and (4) the character of the primary growth cannot be predicted from the roentgenogram.

MacCallum has cited Virchow's dictum that in those organs in which tumors are commonly primary, metastasis seldom occurs, while primary growths are rare in situations which seem to form the best soil for secondary growths. This principle is particularly applicable to the liver, but applies also to the lungs, in which primary malignancy is quite infrequent and secondary malignancy relatively common. Among recent contributions to the subject have been those of Pfahler, Holt and Ratterman, Weil, and Funk. Pfahler, in 216 cases of pulmonary malignancy, found metastatic carcinoma in 196 and metastatic sarcoma in eleven. Of the 196 cases of metastatic carcinoma there were 150 of mediastinal and hilar involvement, twelve were pleural, thirty-four were of the nodular type, and ten of the miliary type. Holt and Ratterman reported a case of metastatic sarcoma, nodular type, proved by necropsy. Weil's case of miliary metastasis, proved at necropsy, was roentgenologically diagnosed miliary tuberculosis. Three of Funk's cases were secondary; two were carcinoma, and one sarcoma.

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Table 1 shows the location and character of the primary lesion with pulmonary metastasis in cases observed at the Mayo Clinic during the last five years. Only cases that can be regarded strictly pulmonary have been included in this series; cases of obviously pleural metastasis and of mediastinal metastasis with apparent projection into the pulmonary hilus have purposely been omitted.

TABLE 1

PRIMARY FOCUS			
	Cases.		Cases.
Breast.....	37	Not found.....	7
Kidney.....	18	Neck.....	6
Thyroid.....	17	Mediastinum.....	5
Lower extremities.....	17	Biliary tract.....	4
Upper extremities.....	12	Rectum.....	4
Testicle.....	10	Pelvis.....	4
Abdomen.....	9	Esophagus.....	3
Stomach.....	7	Chest wall.....	3
Colon.....	7		

Foot, bladder, prostate, larynx, anal region, back, and lung, metastatic to the other lung, each two. Lip, tongue, eye, parotid, brain, jaw, ovary, uterus, vulva, and buttock, each one.

CHARACTER OF PRIMARY TUMOR

	Cases.		Cases.
Carcinoma.....	114	Teratoma.....	3
Sarcoma.....	44	Epithelioma.....	3
Hypernephroma.....	15	Glioma.....	1
Not stated.....	10	Endothelioma.....	1
Lymphosarcoma.....	5		

That the clinical manifestations of pulmonary metastasis are very indefinite is strikingly verified by these cases. In 60 per cent respiratory symptoms were either absent, insufficient to justify mention, or of trivial import. With few exceptions, when pulmonary symptoms were present they were not in proportion to the extent of metastatic invasion. Metastasis from malignancy of the thyroid was, of course, among the chief exceptions. Cough was the most common symptom noted. It was usually dry and hacking, and at first unproductive, although in the later stages in some instances there was a frothy, mucoid, or mucopurulent sputum. Hemoptysis was noted in only a very few cases, pain was not a common symptom in uncomplicated cases, elevation of temperature was rare, and none of the patients gave a history of night sweats. There was also a relative paucity of physical signs, unless pleural effusion was present. Save for anemic pallor the general

physical appearance of these patients was good, and loss of weight, unless the nutritive functions were implicated, was not a constant and notable feature. Eight had gained in weight and twenty-five had lost less than 10 pounds. Ninety-five patients had an average weight loss of 22 pounds.

Thus recapitulation corroborates the view previously expressed that the clinical picture of metastasis in the lungs is inadequate for diagnosis in the majority of cases. Without regard to the location of the primary lesion a roentgen examination of the lungs should always be made, particularly in those cases in which operative removal of the primary growth is intended.



FIG. 241 (Case A319757).—Nodular type of metastasis.

Most textbooks of pathology describe metastatic growths as nodular only. However, roentgenologic experience has demonstrated that there are three types, nodular, miliary, and infiltrative. Dr. H. E. Robertson, Professor of Pathology in the University of Minnesota, states that our roentgen classification is also justified from a pathologic standpoint. With high pulmonary resistance and low virulence of the cancer the nodules are relatively large but few in number; under contrary conditions the lesions are relatively small and the number is vastly increased. The difference is visible roentgenologically antemortem and macroscopically postmortem.

The nodular type of metastasis, which is by far the most common, is ordinarily marked by round, dense, homogeneous areas varying from 0.5 to 6 or 7 cm. in diameter. The borders of the nodules are usually sharply circumscribed, without the hazy zone characteristic of an inflammatory process. Nodules are most often multiple, involving the middle and lower lobes, the apices being quite clear (Fig. 241). While they may be large, it is unusual for them to attain great size without the appearance of other areas; this is a valuable point in distinguishing them from benign lesions. They usually invade both lungs and their multiplicity is also a distinguishing feature. In the cases in



FIG. 242 (Case A149223).—Metastatic nodules with feathery irregular borders.

this series, when one lung only was affected, the right was involved three times as often as the left. While most nodules are circumscribed, they may rarely have a feathery or irregular outline due to the lessened resistance of the lung tissue and the greater virulence of the cancer. Microscopically, the periphery of this type of nodule presents an irregular appearance similar to the infiltrating borders of a primary growth (Fig. 242). Aside from the foregoing exceptions, the distinctive characteristics of the nodular type are the large size, the sharply outlined borders, the multiplicity of nodules, and the involvement of both lungs.

The miliary type of metastasis is marked by a shower of innumerable round or slightly irregular, small, discrete areas of increased den-

sity, varying in size from 4 or 5 mm. to 1 cm., depending on the stage of development. While they are mostly discrete, the overlapping of their shadows may cause a conglomerate appearance. However, it must be borne in mind that the areas grow by peripheral extension and that their confluency is merely accidental. The borders of the individual masses appear to be vaguely delimited from the surrounding parenchyma of the lungs, but stereoscopic examination shows that this appearance is due to the superimposed shadows of the numerous areas. The lesions are often fairly uniformly distributed throughout the lung fields, although in many of our cases the middle and lower lobes were more extensively involved (Fig. 243).



FIG. 243 (Case A248250).—Miliary types of metastasis.

The infiltrative type has been described by roentgenologists who have observed it as an infiltration extending from the hilus along the bronchial markings. No instances of this type were noted in our series. From the description given it would require careful differentiation from metastasis to the mediastinal glands, primary carcinoma originating in the bronchus or mediastinum, pleural metastasis, Hodgkin's disease, syphilis, and various other hilar and mediastinal processes. Pathologists familiar with postmortem study whom I have consulted state that my failure to observe any instance is easy to understand, as the type is exceedingly rare.

Typical cases of either the nodular or miliary type are so striking that they require no elaborate differentiation from other pulmonary lesions. Early and atypical cases may, however, necessitate careful consideration, as differential points cannot be described with precision.

Malignant metastasis confined to the pleura without effusion may give a roentgenologic picture so much like that of metastasis in the parenchyma of the lung that it cannot always be distinguished even by the scrutiny of stereoscopic plates. When fluid is present the pleura is usually thickened, and the whole picture is obscure.



FIG. 244 (Case A142964).—Interlobar effusion. The round shadow is much like that of the individual metastatic nodules in Figure 241, but a metastatic nodule of this size would be accompanied by others.

Lesions which, in varying degree, simulate the nodular type of metastasis include cysts, abscesses, interlobar effusions, Hodgkin's disease, calcium metastasis, and syphilis.

Hydatid or echinococcus cysts are nearly always single and occur most often in the right lower lobe, being secondary to cysts of the liver and gaining entrance through the diaphragm. An unruptured cyst presents a dense, round, sharply outlined shadow. After rupture and partial drainage it may resemble a ring with a translucent center or a cavity partly filled with fluid.

Practically all of our cases of pulmonary abscess show the hazy border characteristic of inflammatory processes and are irregular in shape. In one of our cases of abscess of the lung, confirmed at necropsy, the roentgenogram revealed a single dense area, irregular in outline and so large that the absence of other densities practically excluded malignant metastasis if the existence of the latter was considered at all.

Often interlobar effusions have a wedge-like form with one or more curved borders. An instance of interlobar effusion displayed a well-rounded opacity between the right middle and lower lobes (Fig. 244). There were no accompanying lesions except a large calcified gland in



FIG. 245 (Case A151900).—Syphilis of the lung. Fan-like infiltration, more marked on the right. Confirmation of diagnosis at necropsy.

the left hilus, whose character was evident, and malignant metastasis was not even momentarily considered.

Syphilis of the lung is usually listed among the possible roentgenographic simulants of pulmonary cancer. In one case, proved at necropsy, large patchy fan-like infiltrations, irregular in shape and density, and quite unlike pulmonary cancer, either primary or metastatic, were found in both lungs. Another case, clinically syphilis, was also of the pneumonic type (Fig. 245). A third case presented a large gummatous mass projecting into the hilar region. Association of pulmonary findings with mediastinal and cardiovascular changes shadowed in the

roentgenogram should arouse suspicion of syphilis, and a positive Wassermann reaction will be reasonably convincing.

While the thoracic manifestations of Hodgkin's disease are commonly limited to the mediastinum, in exceptional instances the lung itself may also be invaded and the pulmonary lesions, as seen radiographically, exactly resemble those of malignant metastasis (Fig. 246). Various pathologists have recently been inclined to classify Hodgkin's disease with the lymphosarcomas, and if this becomes the established view any attempt to distinguish them roentgenologically would be superfluous. One of our cases in which there were typical nodules in



FIG. 246 (Case A250092).—Hodgkin's disease. Infiltration extending from the right hilum. Diagnosis proved by biopsy.

the lungs could not be distinguished roentgenologically or grossly at necropsy from those due to other malignancies (Fig. 247).

The "calcium metastasis" of Virchow, which has been fully described by Harbitz, and more briefly by Crane, is, of course, not a malignant process, despite its somewhat suggestive appellation, and in the roentgenogram bears little likeness to pulmonary malignancy. The shadows are smaller than carcinomatous nodules, are often sparse, and their density makes their calcareous nature evident (Fig. 248). We have many examples of this type of metastasis in our plate files.

The differential diagnosis of the miliary variety of metastasis is

much more difficult than the identification of the nodular type. Fortunately, the miliary type is far less frequent than the nodular. Simu-



FIG. 247 (Case A332343).—Nodules in the lung in a case of Hodgkin's disease.



FIG. 248 (Case A224531).—Calcium metastasis.

lants from which it should be distinguished are the miliary type of tuberculosis and pneumoconiosis.

In acute miliary tuberculosis the lesions are more numerous, smaller, and less dense than in miliary metastasis; if the miliary tubercles are associated with chronic tuberculosis the shadows are likely to be more dense because of a deposit of mineral matter in the central necrotic zone. Tubercles grow by forming conglomerate masses and are, therefore, irregular in outline and tend to cavity formation (Fig. 249). In metastasis the growth is by uniform peripheral extension, producing a regular outline. In tuberculosis the tubercles are distributed most thickly in the upper and middle portions of the lung, leaving the bases relatively clear, whereas the areas of metastasis are often most numerous in the lower two-thirds of the lung and the bases are clouded with them.



FIG. 249 (Case A310447).—Miliary type of pulmonary tuberculosis.

The differential diagnosis of metastasis from pneumoconiosis is seldom difficult. Pancoast, Miller, and Landis have noted three stages in the development of pneumoconiosis: (1) increase of hilar and trunk shadows and prominence of the linear markings; (2) mottling throughout the lung structure involving especially the middle portion opposite the hilus, and (3) diffuse, dense fibrosis resembling consolidation. Malignant metastasis is not easily confused with either the first or the third stages of pneumoconiosis, and in the second stage the smaller size and greater number of the mottled shadows, as well as their principal distribution in the middle portion of the lungs distinguish them

rather definitely from miliary metastasis (Fig. 250). The most common mistake is the diagnosis of tuberculosis in cases of miliary metastasis. This may be explained by the comparative frequency of the former. Furthermore, some of our apparent errors may be merely incomplete diagnoses (Table 2).

The credit for teaching that tuberculosis and cancer are incompatible has been given to Rokitansky. Broders, however, has interpreted Rokitansky's teaching to mean an antagonism rather than an incompatibility; he gives an extensive bibliography of observers who have noted the coexistence of the two conditions, and cites 236 cases



FIG. 250 (Case A321973).—Pneumoconiosis.

of concurrence in various organs, adding twenty cases of his own in which both pathologic processes could be demonstrated microscopically in the cervical and axillary lymph glands. Concurrence of pulmonary tuberculosis and metastasis was suspected in several of our cases, and proved at necropsy in one. When such association exists, roentgen differentiation may be very difficult, as one lesion may destroy the characteristics of the other, or only the predominating lesion may be recognized.

Differential indicia derived from our own observations are not advanced as being pathognomonic. It must freely be conceded that atypical cases of pneumoconiosis, miliary tuberculosis, and miliary metastasis may easily be confounded even by an experienced observer. It follows, therefore, that the roentgenologist should be informed with

TABLE 2
DIFFERENTIAL DIAGNOSIS

	Size.	Distribution.	Appearance.
Nodular metastasis.	0.5 to 6 or 7 cm.	Both lungs. Most common in right lung.	Usually large. Dense homogeneous areas. Borders sharply circumscribed.
Miliary metastasis.	4 or 5 mm. to 1 cm.	Uniform throughout the lung with most involvement in the middle and lower lobes. Growth is by peripheral extension.	Innumerable round, slightly irregular discrete areas of increased density. Areas are larger, denser, and less numerous than those in <i>acute</i> miliary tuberculosis. Areas are likely to be less dense and less confluent than the tubercles seen in chronic tuberculosis.
Miliary tuberculosis.	Tubercles smaller than metastatic nodules.	Upper and middle lobes are most frequently involved. Bases are usually clear.	1. <i>Acute miliary tuberculosis</i> : Areas smaller, less dense, and more numerous than in miliary metastasis. 2. <i>Chronic tuberculosis</i> : The tubercles tend to form masses, irregular in outline and denser in appearance than the areas in metastasis. Marked tendency to cavity formation.
Pneumonoconiosis (second stage only).	Areas smaller than in metastasis.	The middle portion of the lungs is mostly involved.	The areas of mottling are less dense and more numerous than in metastasis.

regard to the age, sex, and occupation of the patient, and the presence or absence of a primary focus to correlate with the roentgen findings, or the correlation should be made in conference with the clinician.

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NONTUBERCULOUS INFECTION OF THE LUNGS*

H. MILTON CONNER

I have selected for this review twenty-eight cases of nontuberculous infection of the lungs in which accurate data have been compiled. This number was chosen from a larger series of cases observed in the Mayo Clinic during the period from March, 1920 to December, 1921. This condition has ordinarily been diagnosed clinically as pulmonary tuberculosis or bronchitis. Various authors have named the condition: a lobar type of bronchopneumonia,²⁰ a localized subacute form of bronchopneumonia,¹² chronic progressive influenza,¹³ and, nontuberculous lung infection.^{6, 7, 9} I shall report three cases in detail as illustrative of the findings in my twenty-eight cases.

REPORT OF CASES

Case 1 (A309858). Mrs. O. P. S., aged thirty years, came to the Clinic in March, 1920. The patient had had diphtheria at twenty years, recurrent attacks of tonsillitis, and, in November, 1918, she was in bed three weeks with influenza. During this illness she developed a cough which persisted to the time of examination here. Coughing, which was most persistent in the morning, was more severe during winter and inclement weather and when she was harboring slight infections, such as a "cold," to which she was easily subject. The sputum consisted of a yellowish material and was never profuse. Examination of the sputum elsewhere had failed to reveal bacilli of tuberculosis and a diagnosis of chronic bronchitis had been made.

Examination revealed the blood pressure to be 120 systolic and 70 diastolic; the pulse rate was 72 and the temperature varied from 99 to 98.6. Moist râles were noted at the bases of both lungs, especially abundant on the left. Roentgenograms of the chest showed bronchial infiltration in the right upper lobe, suspicious for tuberculosis. The tonsils were shown to be fibrous with some plugs. The fingers were not clubbed. She was given creosote inhalations with beechwood creosote internally.

The patient was reexamined September 15, 1921. The cough had continued persistent, as much as a quarter of a tablespoonful of yellow pus being raised at one time. Her condition was much the same as at her previous examination and her general health had not depreciated.

Examination of the sputum was negative for bacilli of tuberculosis. Diagnosis was made of chronic bronchitis with nontuberculous infection of the lung, especially in the left base, and very slight bronchiectasis.

* Presented before the Southern Minnesota Medical Association, Mankato, December, 1921. Reprinted from Minnesota Medicine.

Case 2 (A372663). Miss H. B., aged sixteen years, came to the Clinic September 20, 1921, complaining of chronic cough, impaired hearing for five years, and a feeling of being tired. She had had pneumonia in 1909, 1915, and 1918, tonsillitis in 1916, and influenza in 1919. The tonsils and adenoids had been removed in 1920. During her first attack of pneumonia she was very ill in bed for two weeks, following which she developed a chronic cough with expectoration of a yellowish material and a discharge from the nose which persisted to the time of examination here. In 1915 and again in 1918, she developed pneumonia, in 1915 following an attack of measles. During the last two years the cough had become nonproductive until just previous to examination here, when she again began expectorating yellowish material. Expectoration did not reach a maximum at any particular time. The patient "caught cold" easily. There had been no loss of weight, no night sweats, hoarseness, pleurisy, or dyspnea. For a period of six weeks in 1920 she had marked malaise, slight fever, and some loss in appetite and strength. Since childhood she had had severe frontal headaches which came on without cause and were accompanied by a cessation of the nasal secretion. The headaches subsided when the nasal secretions again began to flow.

Examination revealed a rather dull appearing girl with nasal obstruction and snuffles. Her temperature ranged from 98.4 to 99 and the pulse rate varied from 116 to 108. The blood pressure was 112 systolic and 78 diastolic. The fingers were not clubbed. Examination of the heart was negative. On inversion and cough only a small amount of sputum was recovered. There were a few scattered moist râles, but at a later examination on prolonged inversion a moderate number of moist râles were heard in the right base. Examination of the sputum was persistently negative for bacilli of tuberculosis. Sphenoid sinusitis and bilateral maxillary sinusitis were present. The blood showed hemoglobin 65 per cent, 12,800 leukocytes, and 3,910,000 erythrocytes. Roentgenograms of the chest revealed apparently healed tuberculosis of both upper lobes.

Diagnosis was nontuberculous infection of the lung with mild bronchiectasis. The patient was treated by inversion four times a day with beechwood creosote inhalations and beechwood creosote internally. The disease of the sinuses was cared for surgically. Observation has not been sufficiently extended to warrant a statement of the results.

Case 3 (A292384). Mrs. E. M., aged twenty-eight years, came to the Clinic April 10, 1920, complaining of persistent cough and pain in the right thoracic region following an attack of influenza. She had had pneumonia three times, influenza, pleurisy, infection of the antrum, and tonsillitis. The cough developed slowly with gradually increasing severity and frequency, was more troublesome in the morning, and was aggravated by change of position. Sputum, which was expectorated mostly in the morning, was yellowish, rather profuse, and occasionally streaked with blood; there were no frank hemorrhages at any time. Examination of the sputum elsewhere had been negative for bacilli of tuberculosis. There had been some loss of weight, strength, and appetite, and a slight fever. She had had severe pleurisy in the left side of the chest during the attack of influenza and had complained of pain in this region for ten years. There had been some shortness of breath, not asthmatic in type. She had always "caught cold" easily and had had marked nasal catarrh. Her ability to work had been interfered with, but she did not go to bed.

Examination revealed the pulse rate to be 96, temperature 99.4, systolic blood pressure 118 and diastolic blood pressure 78. The fingers were not clubbed. There were abundant moist râles in the right base. Roentgenograms of the chest indicated old tuberculosis in the right apex; roentgenograms of the sinuses were negative. Examination of the nose and throat did not reveal evidence of disease.

The patient was reexamined in December, 1920. She said that the cough had improved when she went home and that expectoration had been slight until six weeks before,

when she took cold. Since then cough and expectoration had been marked. The pain in the left chest had almost subsided. At examination, the area at the left base still showed some evidence of the old condition, but it seemed to be much improved. The cough had entirely subsided by November, 1921.

MAYO CLINIC SERIES

Seasonal incidence.—In most of our cases the disease developed during the colder months; sixteen cases developed during the period from October to April, while only six developed from May to September. The others were indefinite as to time of onset.

Geographical location.—The fact that only three of our patients lived in the South may be of significance, although unquestionably the larger percentage of our registrants come from the North.

Family history.—There was a family history of tuberculosis in eight of our cases, while a similar cough was present in another member of the family in six instances; but only once did I see two patients from the same family. Miller reports in two instances two cases from the same family. Field reports one such instance. In the cases cited by Miller one followed the other, thus indicating direct contagion.

Previous disease.—In most instances the infection followed an acute cold, influenza, or pneumonia. A tendency to "catch cold" easily was quite marked and occurred in twenty-two of our cases. Of minor significance were whooping-cough, measles, scarlet fever, pleurisy, simple grippe, croup, and childbirth.

Accompanying diseases.—Twenty-one patients complained of nasal catarrh, and thirteen showed various nasal abnormalities at examination. Adenoids were noted in only one case, probably because nearly all the patients were adults. Definite sinus disease was found in six of our cases, while in eight there was a history of previous sinus disease. Field states that sinus disease was present in three of his eight cases. Some degree of tonsillitis was found in eight of our cases, and in three others the tonsils had been removed previous to examination here.

Deformity of the chest.—Thoracic deformity was mentioned in only one of our cases, while Field did not find this condition in any of his reported cases.

Bacteriology.—*Bacillus tuberculosis* was absent in all cases in this series and those in the literature. In eleven of our cases the sputum had not been examined previously, while in seventeen it had been found negative for tuberculosis. In 1902, Lord¹² reported twenty-nine cases in which there were cough and purulent expectoration. Eighteen

of these cases were chronic. He studied 100 unselected cases of cough bacteriologically, and was able to demonstrate bacilli of influenza in more or less pure culture in these twenty-nine. Many of his cases were of a type usually classified as chronic bronchitis or tuberculosis. Some of his cases are unquestionably identical with ours. Lord¹³ reported further studies in these cases in 1905. Hamman and Wolman, who dealt with a series of twelve cases practically identical with ours, found that the pneumococcus was most often predominant, next the bacillus of influenza, and lastly the streptococcus. Garvin, Lyall, and Morita, who dealt with eight such cases, found the bacillus of influenza in seven of the eight, predominating in four, and secondary in three. Miller, who reported twenty-two cases which he divided into subacute, subacute with exacerbations, and chronic, found pneumococcus Type IV predominating in ten, the bacillus of influenza in eight, and *Streptococcus viridans* in three. In his seven chronic cases alone, those which correspond to the Mayo Clinic series, the pneumococcus Type IV predominated in four, *Streptococcus viridans* in two, and bacillus of influenza in one; in one case pneumococcus Type IV was predominant in one culture, but a later culture showed predominance of the bacillus of influenza. In Field's cases the bacillus of influenza was predominant in one, *Streptococcus pyogenes* in three, and *Staphylococcus albus* in four. Bossert and Leichtentritt report twenty-four cases which they call "chronic progressive influenza." Their cases resemble ours in some respects. The bacillus of influenza predominated in all their cases. Recently Greely and Brereton reported cultures of *Aspergillus fumigatus*, *Mucor corymbifer*, and *Penicillium glaucum* obtained from nontuberculous infections in the lung, but they apparently were not dealing with the type of case reported in my series. No attempt was made toward a systematic bacteriologic study of our cases, but in those cultured the pneumococcus Type IV, *Streptococcus viridans*, *Streptococcus hemolyticus*, and *Micrococcus catarrhalis* were found predominant. *Aspergillus* was cultivated from one specimen of sputum. Herbst, Elliott, Radin, Hawes, Niles, Lyter, and Butler have also observed similar cases.

Age and sex.—The twenty-eight patients comprising this series ranged from ten to seventy-five years of age with an average age of thirty-nine and seven-tenths years. The disease began in three of Field's eight cases before the age of six; two patients developed the condition at thirteen and three at twenty. Four of Miller's seven

patients whose condition was chronic were more than thirty. Riesman reported seven cases which, however, were of the subacute rather than the chronic variety. His patients were between six and nineteen. Larrabee's cases in symptoms, signs, and location of the lesion resembled those of Riesman. The patients varied in age from ten to seventy-five years. From the literature and from our own cases it may be assumed that the chronic type of case occurs oftener in advanced life, the subacute type oftener in earlier life.

Our cases are almost equally divided as to sex, thirteen males and fifteen females. In Miller's series of twenty-two patients, including all types of cases, there were eight males and fourteen females, while in the seven chronic cases the sexes were more equally divided.

Pathology.—There has been no opportunity in our cases to study the pathology, since none of the patients are known to be dead. Necropsy was performed in one case of Hamman and Wolman; the bronchi of both lower lobes were dilated and filled with purulent material, and around the dilated bronchi were scattered areas of bronchopneumonia. Lord¹³ examined at necropsy one case of forty-four years' duration in which there was slight generalized bronchiectasis with many small areas of interstitial pneumonia. Judging from the physical signs, one would usually expect to find localized bronchitis and bronchiolitis with some dilatation surrounded by small areas of bronchopneumonia and fibrosis, but not sufficient to give signs of consolidation or to produce a good shadow in the roentgenogram.

SYMPTOMS

Cough.—By far the most common symptoms are expectoration and cough over a prolonged period, both occurring either constantly or in attacks lasting a number of days, weeks, or months. All but two of our cases presented these symptoms. In the majority of cases cough was most marked on arising and sometimes on retiring, while paroxysms of cough on stooping, such as are often seen in bronchiectasis, occurred in only a few instances. In most cases the cough was chronic, but increased in severity in the winter. The influence of climate has been variable; only four of our nine patients who moved to a milder climate noticed any benefit.

Expectoration.—The sputum was usually mucopurulent, yellow or yellowish green, and either small or considerable in amount. However,

large amounts were not expectorated at one time, as in bronchiectasis. Sometimes the sputum was streaked with blood and in six of our cases there was definite hemoptysis, in one case as much as a quart of blood was said to be expectorated. In only three cases was the sputum described as of foul odor, while in four others slight odor was noted. It was not of the thin consistency of the sputum of frank cases of bronchiectasis and did not settle into layers on standing.

Pleurisy.—Fourteen of our patients gave histories of so-called pleuritic attacks, but these were not by any means always typical. The complaint of indefinite pains in the chest was not uncommon.

Constitutional symptoms.—As a rule there was very little fever. In the twelve patients with histories of fever it usually occurred for a period of a few days, coinciding with an acute "cold," with the symptoms of acute coryza, and with an exacerbation of the cough. In one of our cases almost the only complaint was recurrent attacks of fever with little or no cough or expectoration. An area in the left base near the angle of the scapula presented the typical physical signs of the disease under discussion. Riesman emphasized the idea that this type of infection may be the cause of obscure fever. Twenty of our patients had symptoms sufficient at times to interfere with work; eleven were at times confined to bed.

A history of chills or chilly sensations was given in nine of our cases. Some loss of weight was noted in fifteen, decrease of appetite in sixteen, decrease of strength and energy in nineteen, and night sweats in ten. Usually none of these symptoms were marked and the patients usually appeared in good general health.

Asthma.—Asthmatic symptoms, sometimes slight, usually not characteristic, occurred in six of our cases, while some dyspnea on exertion was present in nine.

CLINICAL EXAMINATION

The general appearance of the patient was usually good, but sometimes there was a mild anemia, as shown in five of our cases. Some patients had slight curvature of the nails, somewhat resembling the "watch crystal" nails of bronchiectasis or other pulmonary suppuration, but I have not seen any instances of clubbed fingers, which is so prominent a feature in the picture of bronchiectasis.

Inspection of the chest usually produced nothing suggestive, although lessened expansion of the portion involved sometimes occurred or oc-

casionaly a poor or absent Litten's sign on the affected side. The physical signs were located in the right base in eight cases, in the left base in six, in both bases in eight, and in the entire right lung and base of left lung in one. They were fairly well generalized in four cases and the location was not stated in one.

The principal feature of the physical examination was the presence of more or less abundant moist râles, sometimes accompanied by sibilant and sonorous râles. The râles were present mostly during inspiration, sometimes only on deep inspiration, and were often increased by cough or the "expiration-cough-inspiration" method of bringing out râles in cases of tuberculosis. Such râles were present at some time during observation in all of our patients. Occasionally, the râles may be heard over the whole of one lung and often occur in "showers." Sometimes the râles may be brought out by examination after the patient has been in the inverted position for a few minutes, that is, with the head much lower than the hips. Diminished resonance is noted in some of the cases, while in others there is no change in the percussion note. Harsh or diminished breath sounds occurred in some of the cases, but true bronchial breathing and the associated signs of consolidation did not appear. Dyspnea at examination was not noted in any considerable number of our cases. Cyanosis was not observed.

The temperature at examination varied from 98 to 101.8, the pulse from 60 to 130, with an average of 91. The blood pressure in adults varied from 98 to 200 systolic, averaging 127, and from 56 to 104 diastolic, averaging 69.

A leukocyte count from 9,000 to 14,500 was found in twelve of our cases, while a count of 6,000 or less was found in seven. The remainder of the cases were within the normal limits of 6,000 to 9,000.

Roentgen ray.—In most of our cases the roentgenograms were reported negative. Tuberculosis in one or both upper lobes was reported in several instances. Miller found some increase in the pulmonary markings in six of the seven chronic cases. In none of our cases were the roentgen-ray signs of tuberculosis shown in the area presenting the physical signs. In several cases, however, tuberculosis was diagnosed roentgenographically in another area which did not agree with the physical and bacteriologic examination.

In ten instances the patient was not cognizant of a diagnosis previous to our examination; in eleven the diagnosis was chronic bronchitis and in three tuberculosis, and in none of the cases in which a diagnosis

of tuberculosis had been made did we find roentgen-ray evidence of the disease.

DIAGNOSIS

The chief points in the diagnosis of nontuberculous infection of the lungs are: (1) Cough for a prolonged period either constant or with exacerbations, (2) little depreciation of general health, (3) little if any fever, and if present, intermittent, (4) lack of progression of the disease, (5) the lesion usually located in the base of the lung, and (6) absence of bacilli of tuberculosis in the sputum.

DIFFERENTIAL DIAGNOSIS

Nontuberculous infection of the lungs may be distinguished from tuberculous infection mainly by the location of the lesion in the base, by the less marked or absent depreciation in health, by lack of progression, and by the absence of bacilli of tuberculosis. Often there is leukocytosis. In at least nine of ten cases of tuberculosis the infection is found in the upper lobes or apices, while almost the reverse is true of these cases. Recently Rosenblatt reported that in 1,000 cases of tuberculosis only three were primarily in the base of the lung. Seventeen of eighteen patients presenting basilar lesions admitted to the Bedford Hill Sanitarium with the diagnosis of tuberculosis were found to be nontuberculous. In this connection it is well to remember the dictum of Brown that "Abnormal physical signs at one apex should be considered as due to pulmonary tuberculosis until proved not to be; while those at the base should be looked upon as not tuberculous until definitely proved so."

Nontuberculous infection of the lungs is differentiated from simple chronic bronchitis by the fact that chronic bronchitis is usually generalized, is often secondary to cardiac or other disease, has less tendency to the production of purulent sputum, usually does not cause exacerbation of symptoms with temperature, and usually produces no leukocytosis. Moreover, in simple bronchitis the râles are predominantly dry, while in this condition they are predominantly moist.

Bronchiectasis may usually be distinguished from nontuberculous infection of the lungs by clubbed fingers and more abundant foul sputum brought up by paroxysms of cough. Cough and expectoration are usually markedly affected by changes of position, such as lying and stooping. The cough in bronchiectasis is typically loose and a

copious amount of the sputum can usually be produced by inversion. On standing, the sputum often separates into three layers. There is usually no leukocytosis in bronchiectasis.

Bronchopneumonia is usually bilateral, acute, and not recurrent, while this condition is chronic, often unilateral, and recurrent. In bronchopneumonia there are usually some signs of consolidation, while in this condition such evidence is usually absent.

PROGNOSIS

In adults the prognosis must be very guarded, as it is likely that the condition will persist or recur. It seems quite probable that most of these patients will develop a true bronchiectasis if the infection persists. In children the prognosis is somewhat better, according to most authors, although I have not had much experience with such cases.

TREATMENT

Garvin, Lyall, and Morita were the first to emphasize the value of postural treatment, by inversion of the body at least four times daily for a ten or fifteen minute period. This may be done by the patient's kneeling on a chair with the hands on the floor, by assuming the Trendelenburg or reversed Trendelenburg position, or even by hanging the body over the edge of the bed. The more nearly the patient assumes the perpendicular inverted position, the better the drainage usually is. Most of our patients were given steam inhalations with creosote or benzoin two to four times daily; in some instances beechwood creosote was given internally as well. General hygienic measures, such as open air, sunlight, appropriate diet, and moderate exercise, should be instituted.

CONCLUSIONS

1. Nontuberculous infection of the lung is a nonspecific disease which, however, deserves a name as a separate disease entity.
2. The essential features are cough, marked chronicity, exacerbations, little or no fever, and few other constitutional symptoms, usually purulent expectoration, lack of progression, and location of the lesion almost always in the bases.
3. The principal physical sign is moist râles.
4. Diagnosis is made mainly by chronicity of cough, little effect on

general health, location of signs in bases, and persistent absence of bacilli of tuberculosis.

5. In the differential diagnosis chronic bronchitis, tuberculosis, frank bronchiectasis, and bronchopneumonia must be considered.

6. Prognosis must be guarded in adults.

7. Treatment is mainly by posture.

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CLINICAL OBSERVATIONS OF HODGKIN'S DISEASE WITH SPECIAL REFERENCE TO MEDIASTINAL INVOLVEMENT*

WILLIS S. LEMON AND JOHN B. DOYLE

Interest in the affection known as Hodgkin's disease, since its recognition as a clinical entity was established by Wilks¹⁹ in 1865, has been increased and stimulated by extensive study and research. Longcope and Reed have reviewed the development of the history, and little can be added to their reports except the etiologic studies of recent years. Their reports reveal evidence of three great epochs, the age of discovery, the age of uncertainty, and the age of establishing the disease as a pathologic entity.

Wilks defined the disease from the clinical standpoint as it is now known. He pictured it as a gradual and progressive painless glandular enlargement, with anemia and fever, frequently associated with enlargement of the liver and splenomegaly. He also recognized that it progressed constantly until death, usually from exhaustion, and that this progress might be slow, extending over several years, or rapid, of only a few months' duration.

Within the next few years the disease was described by many writers. The names given the disease were almost as numerous as the papers written. They reflected the point of view, either clinical or pathologic, of the observer. This chaos was finally terminated by the researches of Reed, Longcope, and Simmons in 1902 and 1903, who published the description which is now accepted.

A diagnosis of Hodgkin's disease cannot be considered conclusive without the examination of tissue and a microscopic picture in agreement with the clinical description. Twenty-three of the twenty-six patients whose records form the basis of this paper submitted to the removal of glands which microscopically were found to be affected by Hodgkin's disease. The conditions of many other patients were considered admissable by clinical or by roentgenographic examination, but were not sufficiently well diagnosed to belong to this grouping.

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The macroscopic appearance of the glands varied with the duration of involvement, although not necessarily with the chronicity of the disease. A small soft gland might be removed in a chronic case of long standing or a gland much firmer and more fibrous might be removed in a recent case, depending on the duration of involvement of the individual gland resected. The gland, itself, however, in all probability had been involved longer.

The earliest changes were observed in the smaller and more cellular glands and may be divided into four conditions: (1) hyperplasia of lymphoid cells with active proliferation at the germinal centers, (2) increased vascularity, (3) proliferation of the reticular endothelium, often showing mitotic figures in the rapidly dividing cells, and (4) crowding of the lymph sinuses with large and small lymphocytes, polymorphonuclear leukocytes, of both neutrophilic and eosinophilic types, and epithelioid cells. This is the picture of an inflammatory reaction which in the more advanced stages is altered only by a progressive increase in the reticulum which becomes more and more coarse and extensive until the histologic architecture of the gland is completely lost. Within this reticular network, besides the cells already described as filling the lymph sinuses, are the giant cells described by Reed and believed by her to be a development through the epithelioid from the endothelium covering the reticulum. They often appear in large numbers and are of two types, the uninuclears and the multinuclears, whose nuclei are grouped in various positions at the periphery or the center of the cell. The cytoplasm is clear and irregular in contour and the individual nucleus is well bounded by a distinct chromatin outline continuous with a well-defined chromatin network within the nucleus itself. The faintly staining nucleus is made conspicuous by one or several nucleoli which stain deeply. Reed and Longcope are both of the opinion that the uninuclear cell is the parent of the multinuclear; the latter phase is accomplished by repeated division of the single nucleus of the former.

In the chronic cases the entire gland seems to have become fibrous and the cellular elements have become exceedingly few. Adami believes that the formation of lymphomatous nodules in the organs of the body that contain lymphoid tissues is due to this lessening in the number of cells in the glands and is a compensatory reaction. In all of Longcope's cases, even in those in which he believes he saw transformation of preëxisting lymphoid tissue into glands, disease

changes comparable with the foregoing description had already taken place.

Simmons agrees that metastasis in the liver, spleen, lungs, and so forth, can be explained as an attack on the small amount of lymphoid tissue normally present in those organs.

In Case 1 (A134768) of this series such an invasion seems to have occurred, and evidence of involvement could be demonstrated in the skin, glands, pleura, lungs, thymus, diaphragm, liver, pancreas, spleen, and urinary bladder. The glands themselves were entirely replaced by lymphadenomatous tissue with a great increase of fibroid tissue. The histologic picture shows that the disease is caused by an infective agent, the exact nature of which remains unknown. Levin, in discussing the similarity of the disease to cancer, states that the infective agent enters from the surface and attacks the gland because it is the first protective barrier. After the invasion and consequent proliferation in the first glands the subsequent development is analogous to cancer inasmuch as proliferation continues until the death of the patient and the highly specialized function of the original parenchymal cells is lost. He believes that this return to the character of the fetal cell is an evidence of malignancy and places Hodgkin's disease in a borderline position between inflammatory and malignant growths. We believe that the clinical course of the disease (the selection of only one type of tissue in which proliferation occurs) and the almost universal absence of infiltration through the boundaries of the gland indicate an infectious basis. We may add to this the fact that metastasis is a proliferation only of preëxisting lymphoid tissue and does not appear in organs devoid of that tissue.

In recent years Bunting and Yates found a diphtheroid organism which they claim is present in all cases and which may be looked on as the true infective agent. A search for this organism has been made in only a limited number of cases in our series and then only with negative results. Gaarde has made cultures from various glands and has been able to isolate the diphtheroid organism in conditions other than true Hodgkin's disease. So many reports of animal injection have been negative that the method was not resorted to except in one instance, and this with negative results.

Etiology.—In our series of twenty-six patients sixteen worked out of doors and ten worked indoors; their habits of life seemed to be a negligible factor. Seventeen of the patients were males and nine were

females; the average age of the former was thirty-five and four-tenths years and of the latter thirty-three and eight-tenths years. The oldest patient was a woman of sixty-four years, and the two youngest, one male and one female, were twenty. This is contrary to Reed's observation that children are most often attacked, and possibly may be explained by the fact that relatively few children are registered at the Clinic.

Because of the ancient controversy with regard to the importance of tuberculosis as an etiologic factor in Hodgkin's disease, an inquiry was made into the family history of the patients. One patient reported that a cousin had tuberculous glands in the neck, and another patient believed that a maternal aunt had died from pulmonary tuberculosis. Roentgen-ray examination revealed evidence of tuberculosis in only one patient, and this could not be confirmed by clinical or microscopic methods. Moreover, at necropsy no evidence of tuberculosis was found in three examinations, and in only one case was it discovered during the course of the disease. The history of this patient is not included in the present study because no clinical evidence of mediastinal involvement was found. We do not believe that tuberculosis plays a part in producing the disease, and no other infectious disease was found that could be considered a cause.

The examination of the histories revealed that four patients had had diphtheria, but none less than five years before examination. Six had had influenza or grippe, one of whom had been ill one month, and one seven months. All others had been well from actual throat or respiratory disease at least one year. Two had had pleurisy, one and three years before respectively. Three had had bronchitis or pneumonia, but none more recently than eight months, and one thirteen years previously. Seven had had tonsillitis, one many times, but none within a year of examination. Six had submitted to tonsillectomy.

From this report it seems extremely unlikely that recent throat infections are of importance in the etiology of the disease. Moreover, in only one instance was a definite disease condition found in the tonsil. We believe that the occurrence of the condition in the cervical glands has not been accounted for. Reed did not find the report of an authentic case in which the condition had not started in the cervical glands. In our series of cases the cervical glands were involved in 100 per cent, but the latter were not always the first to be affected. It is quite probable that other glands may be primarily involved.

Symptoms.—In most instances the symptoms were typical of cases in which there was no mediastinal involvement. There were, however, a group with symptoms and signs produced by pressure on the structures that traverse the mediastinum. It seemed remarkable that so few patients made complaints that led to the investigation of the contents of the chest, and the absence of symptoms or signs cannot be explained except on the presumption that the glands retain, more or less, their identity, that they are not so hard as malignant tumors or capable of the pressure of an aneurysm, and that they do not infiltrate the tissues around them.

Many of the patients complained of weakness, anemia, loss of weight, night sweats, diarrhea, and anasarca, but such symptoms could not be construed as common to all the patients. Dyspnea, severe enough to be offered as a complaint, was present in six instances. It was found in many other patients who were placed under rigid examination, but this was not considered a fair test inasmuch as twenty-two of the twenty-six patients were under weight and seventeen were definitely anemic, with a hemoglobin reading under 70 per cent. The patients had been ill from two months to eighty-four months; the average was twenty and two-tenths months.

Orthopnea was complained of in two cases.

Pain was complained of in five cases; in the abdomen, in the right shoulder, in the right chest, in the neck and arms, and in the back, respectively. One patient complained of soreness only.

Dysphagia due to esophageal pressure occurred in one case; an indefinite sense of pressure occurred in one; and a headache sufficiently severe to constitute a complaint in one.

Dilated veins over the chest were present in three cases, and over the abdomen and the chest in one. Cyanosis and swelling of the face and the neck was, of course, present in these three cases, and could be easily demonstrated by inverting the patient for a short time. The return of normal color invariably was much later than that of the normal person used as a control. The patients often complained of a sense of fulness in the head during the examination and recalled that they were unable to stoop with comfort. Only one, however, was sufficiently affected to offer this symptom as his complaint.

Tachycardia and palpitation were complained of in two cases and dizziness in only one.

Cough was sufficiently urgent to be a complaint in four cases, and in two the sputum was excessive.

Jaundice, probably from glandular pressure about the common duct, was noted in one case.

Itching skin with variable forms of cutaneous lesions was complained of in four cases. This is in keeping with the many examinations made of uncomplicated Hodgkin's disease. In 20 per cent of our cases this annoying condition was sufficiently severe to make it a chief complaint. These data agree with those of Symmers and of Stokes. We believe that pruritis associated with general adenopathy is a symptom of sufficient importance to call attention to the possibility of Hodgkin's disease as the causative factor.

Fluid was found in the chest, in one thoracic cavity or in both, in eight cases, an incidence of 30.7 per cent. This can be explained by the masses of glands exerting pressure on the pulmonary veins and on the azygos.

It is significant that the recurrent laryngeal, vagus, and sympathetic nerves, and the thoracic duct escaped direct pressure and thus did not provide signs of help in making a diagnosis, also that few of our patients made complaints directing attention to the chest, although in one the right thoracic cavity was found to be filled with fluid. Chyloid fluid was not observed. It may be present. Edsall has described a milky albuminous effusion which contained highly refractile bodies, but a low percentage of fat. Williamson has described a second unusual and interesting finding, pneumothorax preceding hydrothorax. He believed his patient belonged to the group in which the mediastinum is primarily affected.

Boehme, in discussing symptoms and signs, segregated those of the posterior and middle mediastinum from the anterior mediastinum. His observations agree with ours in the infrequency with which enlargement of the posterior glands causes clinical symptoms or signs, and in the frequency with which they are found at necropsy. He, however, calls attention to the finding of dullness over the upper part of the interscapular region and dorsal vertebræ as low as the fourth dorsal spine. Our own experience in attempting to detect the presence of glands by physical means, especially by percussion, has been too discouraging to warrant considering the method of any importance. We believe the distance through that area to be too great and the percussion stroke required too heavy to admit of any accuracy of percussion. We have

had no success in interpretation of D'Espine's sign. It has been absent even in cases of children in whom we were aware of the presence of glandular masses. Dyspnea from tracheal, bronchial, recurrent laryngeal nerve, or vagus nerve pressure, with cough resembling whooping-cough; dysphagia from esophageal pressure; vomiting from pressure on the vagus; and edema of the upper part of the abdomen and serous effusion into the thoracic cavity are to be emphasized. Syncope and cachexia are believed to result more frequently from pressure in the posterior mediastinum than from excitation by a growth in the anterior mediastinum.

We were unable definitely to segregate symptoms and signs, and by this means determine the location in the mediastinum, yet by the regular means of physical diagnosis assisted by the roentgen examination, the location of the disease was ascertained. In this group enlarged glands were discovered in the cervical region in 100 per cent of the cases, in the supraclavicular region in 58 per cent of the cases, in the axillary region in 50 per cent of the cases, in the abdominal region in 19 per cent of the cases, and in the inguinal region in 42 per cent of the cases. Splenomegaly was discovered in 23 per cent of the cases and involvement of the liver in 11 per cent of the cases.

Four patients succumbed to the disease and three necropsies were performed. In each of these (Cases A185298, A249311, and A134768) a diagnosis of mediastinal involvement had been made by clinical methods and confirmed by roentgen-ray examination. In each case the necropsy revealed wide-spread and often unsuspected lymphatic involvement. A short résumé of the necropsy findings in Case A134768 illustrates this observation:*

"On opening the abdomen the stomach and intestines were found moderately distended and the diaphragm at the level of the fifth rib on each side. The liver extended 5 cm. below the ensiform cartilage, 10 cm. below the costal border in the median mammary line on the right, and 4 cm. below the costal margin in the median mammary line on the left. The gallbladder was free and steel blue. The lymph glands in the area of the lesser curvature of the stomach were markedly enlarged. They measured 3 by 5 by 1 cm., were finely granular to the touch, hard, and deep red. The retroperitoneal lymph glands throughout the

* The description of the wide-spread and unusual skin lesion will be omitted since it constitutes a separate report by Stokes with whom one of us (Lemon) was associated in the treatment of the patient.

abdominal cavity were markedly enlarged. They were firm and fibrous, and on section presented a coarsely granular and yellowish-white appearance.

"The liver was increased in size and an area below the right diaphragmatic surface was studded with yellowish-white and dark brown islands; this portion cut with increased resistance and in it only a small amount of liver tissue was discovered.

"The spleen was enlarged and firm, and had a thin capsule, but cut with increased resistance. On section many fibrous bands were found and the pulp could not easily be scraped from the surface.

"The pancreas was enlarged, firm, and coarsely granular, and cut with increased resistance.

"The right kidney was smaller than normal, white, and cut with increased resistance. The pelvis was filled with green slimy pus, and the right ureter was much enlarged and was buried and compressed by the great chain of retroperitoneal glands that lay along the abdominal vessels and their tributaries. Practically the entire kidney was destroyed; the cortical tissue was very thin and the pyramids were much congested.

"The bladder was filled with fluid similar to that found in the pelvis of the right kidney; around the ureteral openings were granular, dark brown masses.

"The only lymphoid tissue in the abdomen that seemed to have escaped involvement was Peyer's patches.

"The right pleural cavity was filled with straw-colored fluid; the lung was moderately contracted and lay near the spinal column. Fluid was also present in the left thoracic cavity. A mediastinal mass, firm and nodular, measuring 6 by 7 by 6 cm. was found. The right parietal and diaphragmatic pleura was studded with small granular masses and the intercostal spaces seemed to be crowded with similar nodes. The aorta could not be seen since it was surrounded on all sides by a continuous chain of yellowish-gray glands of moderate firmness. When this mass of glands was cut through the aorta was exposed. It showed a smooth and shining normal intima."

Sections were taken from the heart, lungs, liver, kidney, spleen, pancreas, suprarenal, thymus, diaphragm, and lymph glands, and all except the suprarenal, the kidney, and the heart were found to present the pathologic picture described.

Before the patient's death specimens had been examined from the

arm, the wrist, the groin, and the glands; they too presented the typical picture of Hodgkin's disease.

Up to the time when the chest began to fill with fluid and necessitated repeated aspirations, the patient had been working regularly. He had been under observation by Dr. Stokes almost continuously for three years.

Despite the extensive disease of the lymphoid structures, there were few symptoms until within a short time of death, and no hint of the destruction of the kidney, except the presence of pus cells in the urine. Although signs were present, symptoms that might call attention to the wide-spread disease in the thorax were wanting.

Lyon has reported a case of Hodgkin's disease with perforation of the wall of the chest. He noted the wide-spread invasion of the lymphoid tissue. We have seen but one similar case; the patient is still alive and under observation; it is not known whether the granuloma of the chest wall is continuous with the glands that are so markedly enlarged in the mediastinum (Table 1).

Blood counts were made in twenty-three cases; no material changes from the normal were noted. In Case A134768 the eosinophils were numerous, but it was thought that the extensive cutaneous lesion may have influenced their proportion. In none of the cases was there indication of an increase in large mononuclear cells, as described by Bunting, nor of an excess of lymphocytes that is so general in late stages of the disease. Levin gives a very interesting explanation for this excess. He believes that the terminal lymphocytosis is due to a crowding full of all the lymphoid tissues and an overflow into the blood stream. He admits, however, that usually the blood picture in Hodgkin's disease is normal. The report of the blood findings would have been more satisfactory if it had been possible to make repeated counts on each patient.

Because the deeper glands may be primarily involved and because their presence may be recognized by clinical examination only with great difficulty, the roentgen ray is used to assist in the diagnosis of mediastinal involvement. Wessler and Greene have reported their results with the roentgen ray and have attempted to form four groups of cases according to the types of shadows: Group 1, the mediastinal tumor type; Group 2, the infiltrative type; Group 3, the isolated nodular type with involvement of the hilus, and Group 4, the nodular type presenting at the root of the lung. Wessler and Greene also call atten-

TABLE 1
BLOOD FINDINGS IN CASES OF HODGKIN'S DISEASE*

Case.	Date.	Hemo- globin.	Erythro- cytes (millions).	Leuko- cytes.	Polymor- phonu- clears.	Lympho- cytes.	Large mono- nuclears.	Eosino- phils.	Raso- phils.	Aniso- cytosis.	Poikilo- cytosis.	Tempera- ture, F.
184768	July 2, 1915.	80	4.4	23,900	48.0	23.3	4.3	27.7	0.7			99.2
185298	February 19, 1917.	50	3.77	12,800	31.7	9.3	7.7	1.0	0.5			98.4
185390	February 10, 1917.	65		5,200								98.4
185465	February 12, 1917.	85	4.72	5,200	59.7	30.7	9.0	0.0	0.7			98.4
185523	February 12, 1917.	57	3.25	2,000	96.7	5.7	6.7	0.7	0.3			98.2
185736	May 31, 1917.	61	3.72	7,000	78.7	12.7	5.0	3.7	0.0			98.6
201189	July 12, 1917.	88	4.88	13,002	81.0	10.0	6.3	2.0	0.7			97.8
209443	October 1, 1917.	70	5.24	8,600	50.0	36.3	10.0	2.7	1.0			99.0
211906	October 18, 1917.	68	4.04	8,200	50.0	8.7	3.0	3.3	0.0			99.8
219918	January 25, 1918.	64	4.51	23,000	55.0	18.0	15.3	0.0	1.0			98.8
220896	February 1, 1918.	64	4.06	10,000	65.7	6.7	6.3	2.0	0.0			100.4
228184	May 21, 1918.	70	4.4	12,200	85.0	6.7	4.7	3.3	0.7			99.2
240373	October 31, 1918.	25	3.76	8,600	86.3	5.0	4.5	1.5	0.0			101.0
240511	November 21, 1918.	47	3.26	16,400	89.0	6.5	5.5	0.0	0.0			98.2
253208	February 10, 1919.	70	4.88	19,500	83.6	9.5	5.5	2.0	0.0			98.4
253761	November 26, 1919.	74	4.72	15,800	83.0	12.0	4.0	2.0	0.0			98.2
260923	March 19, 1919.	55	3.76	7,800								98.2
260948	March 28, 1919.	58	4.4	8,400								98.2
263233†	March 29, 1919.	53	4.4	49,000	90.0	5.0	5.0	0.0	0.0			98.4
268832	April 24, 1919.	45	3.46	8,600	84.0	11.5	3.5	1.0	0.0			99.0
273780	June 6, 1919.	68	4.26	17,400	76.0	19.5	3.5	1.0	0.0			99.6
274527	June 10, 1919.	62	4.8	10,200	87.5	7.5	5.0	0.5	0.0			99.6
301897	January 7, 1920.	50	4.24	15,400								99.6
Average		67	4.23	13,370	77.7	13.2	6.1	2.9 for 18 cases; 1.5 for 17 cases	0.3			

* Cases 202416, 247053, and 262293 are omitted because blood counts were not obtained.

† Patient was in extrema. Death April 18, 1919.

tion to the early involvement of the paratracheal group of glands and regard a shadow in that area as very significant.

This grouping is useful, but in general Hodgkin's disease is suspected when the roentgenogram reveals a bilateral feathery shadow passing outward from each hilus. A pathologic diagnosis hardly should be expected from the roentgenographic findings, but in eight cases a positive opinion was reached. In four cases the picture was complicated by the presence of fluid; in four the presence of glands was recognized, but their character was undefined. In three a suspicious shadow or thickening was seen; in one the diagnosis was sarcoma; in five the shadow was reported as that of a mediastinal tumor; and in two no positive conclusions were reported.

The roentgenogram must be considered a routine method of examination inasmuch as it is essential to know of mediastinal complications both from the standpoint of prognosis and of treatment.

Besides the usual treatment, which is comparable with that used in chronic tuberculosis, many patients have been treated with radium. The glands respond most satisfactorily. Treatment by the roentgen ray probably offers most in mediastinal complications and we have used it in a limited number of instances with satisfaction. It results in a replacement by connective tissue and a diminution in the size of the glands. This is particularly true of glands that are still soft and have not passed into the fibrous stage. The improvement in the patient's general health and appearance is out of proportion to the effect of the treatment on the glandular masses. These facts have recently been illustrated strikingly in a patient now under treatment. Treatment should be begun even before the deeper groups of glands can be palpated and should be kept up for a long time in association with radium, which is more useful over the superficial glands.

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THE DIAGNOSIS AND TREATMENT OF TUBERCULOUS EMPYEMA*

CARL A. HEDBLÖM

Tuberculous empyema may be defined as a type of suppurating pleurisy in which the tuberculosis bacillus is either the sole infective organism or is one of the organisms of a mixed infection. Dry adhesive pleuritis, pleurisy with serous effusion, and suppurative or hemorrhagic pleurisy constitute different grades of reaction to pleural infection. The extent of the pleural reaction is in proportion to the virulence of the infection and the resistance to it.

From a pathologic point of view tuberculous pleurisy may be subdivided into primary and secondary forms. To the first belong the cases of initial involvement of the pleura; to the second, cases following lesions of the lungs, chest wall, or glands. Some writers consider all cases of tuberculous pleurisy secondary to pulmonary involvement. Cases occur, however, in which there is no demonstrable focus in the lung. In such instances the lung tissue possibly furnishes only the avenue of infection.

Primary tuberculous pleurisy with or without effusion, which has its analog in primary tuberculous peritonitis, probably occurs more frequently than is generally recognized. Hodenpyl found nodules and patches on the visceral pleura in forty-four of ninety-one cases in which the lungs were free from tuberculosis. These nodules were proved to be tuberculous by microscopic examination in forty-one cases, and in three without nodules foci of tuberculosis were demonstrated microscopically. Hodenpyl regards this type of involvement as the most likely to heal spontaneously. To the same group belongs probably a large proportion of the cases of primary adhesive pleuritis and pleurisy with effusion. The analogy to tuberculous peritonitis of the dry plastic and ascitic types is striking.

The question of the etiology of primary or idiopathic pleurisy with effusion is of especial importance in the consideration of tuberculous empyema. Although Cabot, Rist, and Webb expressed doubt with regard

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to the tuberculous nature of the primary serous effusions observed in the American Expeditionary Forces, there is much evidence to substantiate the view commonly accepted, that save for an occasional instance of effusion complicating unrecognized pneumonia, these are tuberculous in nature. This evidence is furnished by the investigation of the further history of cases of pleurisy with effusion, and by a study of the fluid. Series of patients whose course is followed for from five to twenty years show that from 35 to 55 per cent eventually die of tuberculosis (Osler, Hedges, Sears, and others). Insurance companies find that deaths from tuberculosis among persons having had pleurisy with effusion is three times the average (Norris and Landis). Of special interest is a series of Köster, who found that of 514 patients 245 became tuberculous. About 50 per cent of the patients had active lesions before the end of five years, but a latent period of ten years or more was noted in about 7 per cent of 164 cases.

The demonstration of tuberculosis bacilli in the serous exudate constitutes the most convincing evidence of its tuberculous nature. Direct examination of the sediment obtained by centrifugalizing the digested clot, the so-called inoscopy of Jousset, and animal inoculation, have yielded positive results in from 20 to 85 per cent of the cases. The widely divergent results are probably due to differences in technic, and in the animal inoculations, to the varying virulence of the bacilli. By inoscopy positive results were obtained in 20.8 per cent in a series of 115 cases at the Massachusetts General Hospital (Goodall); in 65 per cent by Zebrowski; in 45.4 per cent in a series of fifty-one cases reported by Musgrave, and in 100 per cent in twenty cases reported by Jousset. Animal inoculation yielded only 33 per cent positive results in Musgrave's series, but Daminy, using 300 c.c. of exudate in divided doses of 10 c.c. each, obtained positive results in forty-eight of fifty cases. Spengler states that he has always been able to demonstrate tuberculosis bacilli by using 200 c.c. of exudate aspirated from the lowest portion of the pleural cavity. Musgrave demonstrated the bacilli by inoscopy in eight cases in which the guinea-pig test was negative. The varying virulence of the bacilli is indicated by the fact that he obtained negative results in three animals injected with three successive tappings, but six months later obtained a positive result. Barjome and Cade also found that only one of three or four animals gave a positive test. These experiences emphasize the uncertain significance of a single injection of a few cubic centimeters of fluid in one animal.

Musgrave regards a positive tuberculin test and a relatively large percentage of lymphocytes in the exudate as of diagnostic value.

A serous effusion may persist for months and recur after repeated tapping (Fyfe), or it may promptly subside after one or two aspirations. Patients should not be repeatedly tapped, however. If the effusion persists it may remain serous, or, as often happens, especially after frequent tapping, it may become purulent. Very little seems to be known regarding the conditions which govern these changes. Floyd concludes from an experimental study, injection of dead and living pyogenic bacteria into the pleural cavity, that the varying reactions depend on the relative virulence of the organism, and that when there is but little chemotaxis pleurisy with or without effusion results, but that if the chemotactic action is profound and the elaborated toxin not too destructive, empyema results. Opie, on the other hand, using graded amounts of turpentine as the pleural irritant, which produces effusion, found an increased tendency to purulent change following aspiration of the fluid. He believes that this difference may be due to an increased activity of the leukoprotease of the polynuclear leukocyte normally held in check by the anti-enzyme of the exuded serum.

In contrast to the cases of primary idiopathic pleurisy are pleurisy in the lung, chest wall, or glands. The common pneumonic pleurisy with or without effusion is an analogous condition. Lord found a serous effusion in 5.2 per cent of 1,185 cases of pneumonia, and Musser reports five serous and twenty purulent effusions in 127 necropsies following pneumonia. In the recent epidemic of streptococcus infection pleural effusion was the rule.

Tuberculous infection of the pleura is a common concomitant of pulmonary tuberculosis. Osler writes that the visceral pleura is always involved. The frequent resultant partial obliteration of the pleural cavity may account for the fact that a relatively large proportion of cases do not develop late effusion. In the absence of obliterating adhesions the pleural cavity may become grossly infected by the rupture of a subpleural focus, producing a spontaneous pneumothorax. This occurs in from 4 to 10 per cent of institutional cases of tuberculosis (Gutmann, Eichhorst, Cruice). The presence of apical pleurisy should be considered as a benignant process of conservation. This complication is usually announced by marked symptoms. A mixed infection usually results, which makes the prognosis grave. Spontaneous pneumothorax, however, may have an insidious onset, and not give rise to

marked symptoms. Such cases are of the "latent, mute" type of pneumothorax which are most liable to develop a purulent effusion (Bouchut and Gravier). Bäumlér reports two cases in which the exudate remained serous in the presence of pneumothorax.

Tearing the lung by bandlike adhesions occurs as a complication of the pneumothorax treatment of pulmonary tuberculosis (Cocke, Marshak and Craighead, Webb, and others). Duboff reports ten cases of effusion in forty-eight of which artificial pneumothorax had been used. Spengler states that an effusion resulted in 50 per cent of 100 such cases. He believes that the exudation is due to loosening up of pleural adhesions.

The bacteriology of undrained tuberculous empyema has been less well studied than has that of tuberculous pleurisy. Netter,⁵⁹ in a series of 109 cases of purulent pleurisy, found tuberculosis in 15.2 per cent, but in thirteen cases diagnosed tuberculous empyema he found the bacilli in only five (Sokottowski). In six cases there was no growth. He regarded the cases which were sterile to culture as tuberculous. Ehrlich found tuberculosis in seven of nineteen cases of empyema, Fraenkel found it in one of twelve cases, and Renvers in two of fifteen cases. Netter writes that one always should obtain positive results in tuberculous empyema either by guinea-pig inoculation or by direct examination. Staphylococcus in pure culture is uncommon, but when present is suggestive of tuberculosis (Netter, Sokottowski). A sterile purulent effusion is tuberculous in the majority of cases (Sokottowski).

In chronic draining empyemas bacteriologic study is of little value. Beck⁶ reports staphylococci in practically all cases and streptococci in 10 per cent. Gordon, in an intensive study of twenty-five chronic cases, concludes that the primary organism, notably streptococcus, disappears, and that there may be a succession of secondary invaders. It seems evident, however, that although a mixed infection always occurs in these drained cases, the tuberculous infection persists. Beck³ states that tuberculosis is rarely found in secretions even in cases in which the empyema is positively of tuberculous origin, but that the bacilli may be demonstrated in numbers in the exudate after treatment with bismuth paste, which he believes stimulates leukocytosis, the leukocytes carrying the bacilli out in the discharge. Heuer refers to a case in which bismuth paste was used, after which the exudate teemed with bacilli.

DIAGNOSIS

Positive proof of the tuberculous nature of a purulent exudate is afforded by finding the bacilli in the exudate by direct examination, by



Fig. 252 (Case A185290).—Chest shown in Figure 251 following a Wilms three-stage plastic operation. Complete obliteration of the cavity, April 7, 1920.

Fig. 251 (Case A185290).—Chronic tuberculous empyema of about three and one-half years' duration with almost complete collapse of the lung, September 10, 1919.

animal inoculation, or by a demonstration of the characteristic microscopic picture in the excised pleura (Figs. 251, 252, 253, and 254).

Unfortunately the demonstration of the bacilli in the exudate is usually difficult, and the animal inoculation test results in many failures and

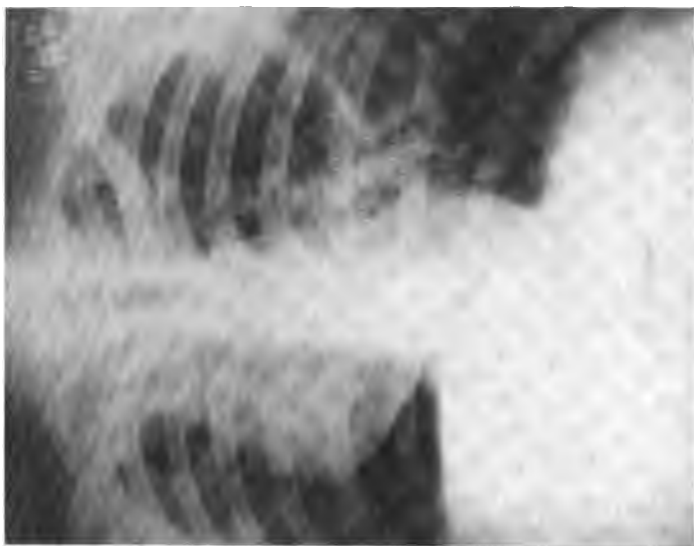


FIG. 254 (Case A341738).—Chronic tuberculous empyema cavity of two years' duration.

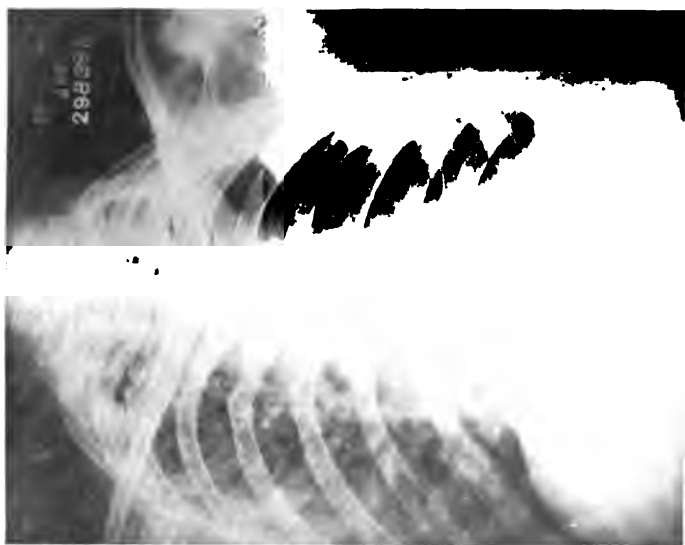


FIG. 253 (Case A298385).—Chronic empyema cavity of sixteen years' duration.

requires at best six weeks of time. The examination of pleural tissue is a postoperative procedure. In the ordinary case, therefore, a presumptive diagnosis must be made on the clinical history of the case,

the character of the exudate, and the recognition of a tuberculous process in some other organ.

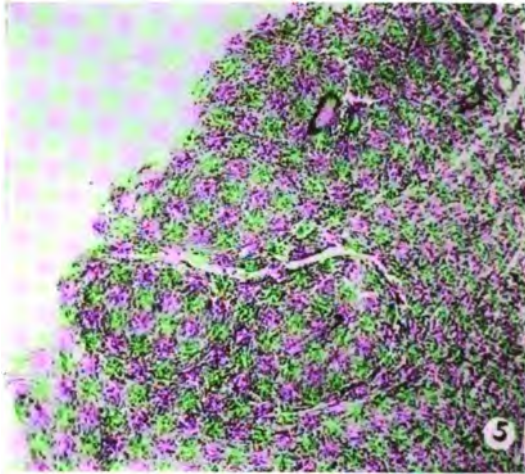


FIG. 255 (Case A47717).—Typical tubercles and foreign-body giant cells associated with marked lymphocytic infiltration in a tuberculous area in the parietal pleura.

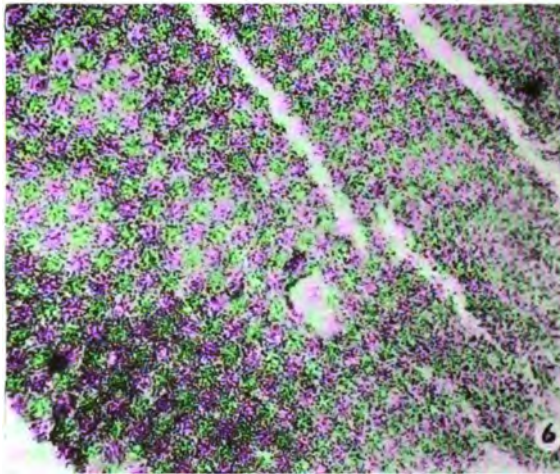


FIG. 256 (Case A185290).—Ill defined tubercles and foreign-body giant cells associated with marked lymphocytic infiltration in a tuberculous area in the parietal pleura.

History.—A family history of tuberculosis is of some value. Cabot showed that in a series at the Massachusetts General Hospital of 300 patients with pleurisy 67 per cent who later developed tuberculosis

had a positive family history, while only 25 per cent of those who remained well had such a history. An insidious onset without preceding

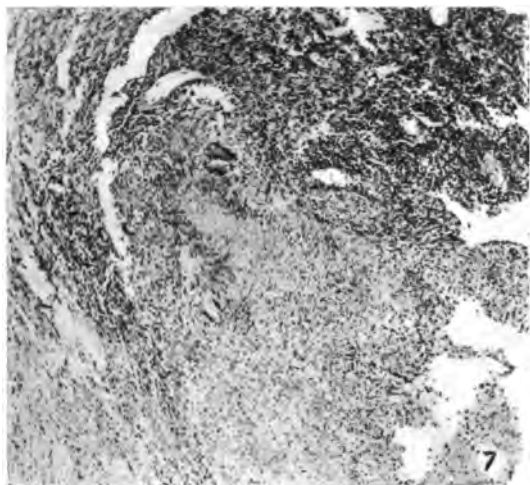


FIG. 257 (Case A362614).—Few foreign-body giant cells associated with marked necrosis, lymphocytic infiltration, and fibrosis in a tuberculous area in the parietal pleura.

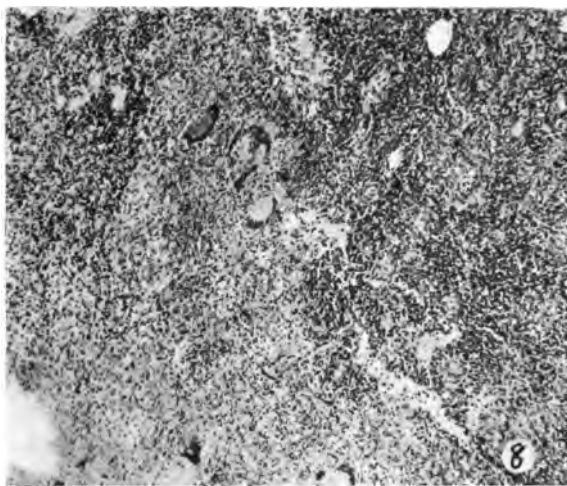


FIG. 258 (Case A289416).—Ill defined tubercles and foreign-body giant cells in an area of tuberculous granulation tissue of the parietal pleura.

infectious disease, especially if accompanied with fever, night sweats, loss of weight and strength, loss of appetite, and progressively increas-

ing nervousness, is always suggestive of tuberculous infection. The cases with insidious onset in apparently healthy, robust persons are among the most difficult to recognize. A history of preceding pleurisy with effusion, even though years before, affords grounds for suspicion that a later "idiopathic" empyema may be tuberculous. A history of pleurisy with serous effusion in an adult should be evaluated equally with that of an hemothysis (Lemon).

Character of exudate.—In cases without drainage, sterile, purulent fluid, especially in the presence of fever and with a low leukocyte count, is almost certain to be tuberculous. Staphylococcus infection, ordinarily rare in undrained empyema, has been found associated with tuberculosis. A pyogenic organism, notably pneumococcus, may die, but an effusion giving a negative culture and smear may be considered tuberculous.

The presence in other organs of a tuberculous lesion, notably pulmonary phthisis and tuberculous peritonitis, lends weight to a presumptive diagnosis of the tuberculous nature of coexisting empyema. A healed or quiescent pulmonary process such as is often seen in the roentgenogram is probably, taken by itself, of relatively little significance, but an active process giving rise to characteristic râles, and especially positive sputum examination, leaves little room for doubt with regard to the tuberculous nature of an idiopathic purulent effusion. Effusion complicating artificial pneumothorax therapy, or following spontaneous pneumothorax in advanced cases, is probably tuberculous, even in the presence of pyogenic organisms, which in such cases contribute to a mixed infection. Fagioli reports a serous effusion in ten of twenty-three cases in which pneumothorax therapy was used.

MAYO CLINIC SERIES

The records of the Mayo Clinic since 1910 contain histories of twenty-three cases proved by bacteriologic or pathologic examination to be tuberculous empyema. These cases are included in Group 1. Fifty-one cases not so proved, but in which a tuberculous lesion elsewhere, or other clinical features, make for at least a probable diagnosis of tuberculous empyema, have been classified into Groups 2, 3, and 4.

Group 1.—In the twenty-three patients in this group the diagnosis was made or was confirmed by examination of excised pleural tissue in eighteen. Guinea pig inoculation of the exudate was positive in one

in the purulent stage and was positive in one in the serous stage; necropsy in the latter case showed pyopneumothorax, and tuberculosis of the lungs, liver, and retroperitoneal glands. Tuberculosis bacilli were found in smears of the purulent exudate in three. Five patients had well-marked tuberculous lesions, associated with Pott's disease of the spine and multiple "cold" abscesses in one, tuberculous glands proved microscopically in one, and in one necropsy showed, besides, a large pulmonary cavitation, tuberculosis of the kidneys and multiple tuberculous ulcers of the intestines, from the perforation of one of which the patient had died. In the fourth the onset was that of a typical pleurisy with effusion, and in the fifth the sputum contained tuberculosis bacilli.

Group 2.—In this group were sixteen patients with clinically tuberculous empyema. Further evidence substantiated the presence of tuberculosis. In one patient (Case A51816), besides a history of pleurisy with effusion, chronic cough with sputum, and a diagnosis at operation, "cold" abscesses developed later in the chest wall. In two (Cases A137779 and A260196) characteristic lesions were found at necropsy, and in one besides cough, sputum, and physical signs of phthisis, hemoptysis, developed. In the remaining twelve various combinations of positive findings as to family history, past history of pleurisy, cough with sputum, physical and roentgen-ray findings, the gross appearance at operation, and the further course, leave little question of the presence of tuberculosis.

Group 3.—There were twenty-two patients with empyema associated with pulmonary tuberculosis in this group. Roentgen-ray showed the pulmonary lesion in all. In three there was an active process at the time of the first examination, and in four later examinations showed active progressive lesions. The bacilli were found in the sputum in four with active pulmonary foci, and in one without such foci. There was a positive family history in two; in both the lesions were active. A history of pleurisy or "cold" preceding the empyema was noted in six, and a past history of pleurisy was noted in nine, in three of which the immediate preceding illness was not characterized by pleurisy. The onset of the empyema was insidious in three, and sudden in fourteen. The onset was preceded by pneumonia in ten. There were various combinations of cough with sputum and fever in sixteen, and there were râles or bronchial breathing, or both, in six, in two of which there was no cough or sputum.

GROUP 1
TUBERCULOUS EMPYEMA

Case.	Sex and age.	Pleurisy.	Illness at onset.	Onset sudden or insidious.	Cough.	<i>Bacillus tuberculosis</i> in sputum.	Rales.	Röntgen-ray findings.	Previous operation.	Diagnosis of tuberculosis.	Operations.	Pathologic diagnosis.	Remarks.
A47717	M. 45	0	Influenza.	S.	+	+	..	Fluid.	7 aspirations.	0	2/18/19 Plastic, resection of three ribs, after Dakin's solution treatment. 5/2/19 Skin plastic.	5/2/19 Tuberculosis of parietal pleura.	2/20 Complete healing.
A34092	M. 26	+	Pleurisy.	S.	+	+	..	Right tuberculosis; thickened pleura; left effusion.	6/09 Drainage.	..	6/10/11 Drainage (mixed tuberculous infection).		1914 Death. Empyema never healed; patient had pulmonary tuberculosis.
A101014	M. 39	+	Pleurisy.	S.	+	..	..	Retraction.	5 aspirations; rib resection.	+	2/27/14 Partial Schede. 10/6/15 Skin plastic. 6/28/17 Aspiration pleural abscess.	6/17/16 Tuberculosis of parietal pleura.	Multiple "old" abscesses; Pott's disease. 1/9/19 Death from influenza; no necropsy.
A107204	F. 26	0	Pneumonia.	..	+	+	..	Old tuberculosis; bronchial thickening.	1914 Aspiration; tuberculous glands.	..	8/21/17 Drainage.		8/17 Death from septicæmia; no necropsy.
A111007	M. 36	0	Abscess.	S.	+	..	..	Right empyema; thickened and retracted pleura.	7/13 Rib resection.	0	7/29/14 Drainage. 4/24/15 Multiple rib resections. 7/8/15 Minor Schede.	7/2/15 Tuberculosis of parietal pleura.	1917 Last report; good health; slight drainage.
A111478	F. 18	0	Pneumonia.	S.	+	+	+	Fluid; thickened pleura.	5 aspirations.	0	8/4/14 Rib resection for drainage. 4/17/15 Incision for drainage. 8/20/19 Exploration, no cavity found.	4/17/15 Tuberculosis of parietal pleura.	8/21 Wound still draining.
A110106	M. 40	+	Pleurisy.	S.	+	+	..	Left empyema; thickened pleura.	9/13 Rib resection.	0	9/29/14 Drainage. 8/6/15 Schede operation. 12/17/15 Rib fragment removed.	12/17/15 Tuberculosis of parietal pleura.	6/16 Wound almost healed; good health.

A130190	F. 15	0	0		I.	+	+	+	+	Empyema; thickened pleura; lung retracted.	10/14 Aspiration; rib resection.	+	6/9/16 Rib resection for drainage.	3/30/16 Tuberculosis of parietal pleura. 6/7/16 Tuberculosis of parietal pleura.	8/17 Wound healed; no trouble since.
A149126	M. 40	+			I.	+	+	+	+	Fluid; left lung collapsed; tuberculosis right.	1914 12 aspirations.	+	1/7/16 Rib resection for drainage.	1/4/16 Tuberculosis bacilli in pleural exudate.	7/16 Death.
A165637	M. 44	0			S.	0	+	+	+	Right empyema; large pocket.	3 rib resections.	0	6/20/16 Exploration after Dakin's solution treatment. 8/9/19 Schede.	8/9/19 Tuberculosis of parietal pleura.	9/10/19 Death; lung abscess, bronchial fistula, tuberculous empyema, tuberculous meningitis. No necropsy.
A185290	M. 38	+			S.	0	0	+	+	Upper left tuberculosis; fluid.	3/18 Drainage.	+	8/12/19 Exploration and curetage; preliminary Dakin's solution treatment. 3/16/20 Wilm's first stage, after Dakin's solution treatment. 3/25/20 Wilm's second stage. 5/30/20 Wilm's third stage.	4/2/17 Tuberculosis by guinea pig inoculation. 8/12/19 Tuberculosis of parietal pleura.	3/21 Good health; slight drainage.
A217107	M. 53	0			I.	+	+	+	+	Tuberculosis both apices; fluid.	Aspiration.	+	12/24/17 Rib resection for drainage.	12/17 Tuberculosis of parietal pleura.	12/27/17 Death. Necropsy; perforation tuberculous ulcer of ileum; multiple tuberculous foci.
A230390	M. 21	0			S.	+	+	+	+	Fluid; heart enlarged.		0	9 Aspirations. 6/22/18 Rib resection for drainage; septic pyopneumothorax.	6/24/18 Tuberculosis by guinea pig inoculation.	6/28/18 Death. Necropsy; tuberculosis both lungs; liver, retroperitoneal glands.
A251743	M. 22	0			+	0	+	+	+	Lung retracted; right pneumothorax; fluid.	3/17 Aspiration; drainage.	0	12/12/18 Decortication after Dakin's solution treatment. 3/4/19 Rib resection for drainage. Patient refused extensive plastic.	3/4/19 Tuberculosis of parietal pleura.	4/21 Wound still draining; treatment incomplete.
A260767	M. 32	?			I.	+	+	+	+	Infiltration left lung.	1913 Abscess left axilla.	0	2/27/19 Exploration. 3/6/19 Negative aspiration. 3/30/19 Negative aspiration. 7/17/19 Rib resection for drainage.	7/17/19 Tuberculosis of parietal pleura.	Much improvement when last seen. Developed pulmonary tuberculosis, apparently as secondary complication.

TUBERCULOUS EMPYEMA—Concluded

Case.	Sex and age.	Pleurisy.	Illness at onset.	Onset sudden or insidious.	Cough.	<i>Bacillus tuberculosis</i> in sputum.	Rales.	Röntgen-ray findings.	Previous operation.	Diagnosis of tuberculosis.	Operations.	Pathologic diagnosis.	Remarks.
A262614	F. 27	+	Pleurisy; child-birth.	I.	+	..	..	Fluid.	2 Aspirations; rib resection.	0	3/25/19 Decortication after Dakin's solution treatment. 3/1/21 Rib resection and skin muscle plastic (bronchial fistula).	3/25/19 Tuberculosis of parietal pleura. 3/1/21 Tuberculosis of parietal pleura.	4/21 Wound practically healed.
A263092	F. 21	+	Pleurisy; child-birth.	I.	..	+	+	Lung collapsed; probably fluid.	2 Aspirations. 12/18 Drainage.	0	3/27/19 Decortication attempted. 11/19 Rib resection for drainage.	12/19 Tuberculosis smear and pleura.	12/19 Death from hemorrhage.
A263570	M. 27	+	Pleurisy.	S.	+	+	..	Probable empyema, left tuberculosis; interlobar pleurisy.	6/18 Drainage.	0	3/18/19 Exploration after Dakin's solution treatment. 3/27/19 Rib resection and skin plastic.	3/27/19 Tuberculosis of parietal pleura.	5/20 Death.
A274637	M. 54	+	Influenza.	S.	+	..	..	Pleural thickening; probably fluid.	2/19 Drainage.	0	6/28/19 Rib resection for drainage.	6/28/19 Tuberculosis of parietal pleura.	9/20 Slight drainage; patient working.
A280416	M. 54	+	?	I.	+	+	..	Left empyema, small pocket.	1909 11 Aspirations. 1918 Drainage.	0	10/16/19 Decortication after Dakin's solution treatment. 10/19/20 Rib resection and skin muscle plastic.	10/19/20 Tuberculosis of parietal pleura.	4/21 Wound healing; some pain.
A333166	M. 20	+	Pleurisy; influenza.	..	+	+	+	Pleurisy.	12/19 Rib resection. 2/20 Drainage.	0	9/14/20 Aspiration; preliminary Dakin's solution treatment. 10/4/20 Rib resection and skin muscle plastic.	10/4/20 Tuberculosis of parietal pleura.	10/10/20 Appendectomy; sanguinous appendix. 4/21 Patient in sanatorium; drainage; high temperature, and so forth.
A333476	M. 20	+	Influenza; pleurisy.	I.	0	+	..	Density; abscess.	8/19 Rib resection.	0	10/14/20 Decortication after Dakin's solution treatment. 12/9/20 Rib resection and skin plastic.	12/9/20 Tuberculosis of parietal pleura.	3/21 Health good; wound healing slowly.
A340048	M. 30	0	Influenza.	I.	+	+	..	Empyema; lung collapsed; fluid in right lung.	Aspiration; drainage; wound reopened.	0	12/21/20 Rib resection and skin muscle plastic.	12/21/20 Tuberculosis of parietal pleura.	4/21 Narrow sinus; progress good.

Group 4.—The patients in this group had empyema following idiopathic pleurisy with effusion. They gave histories of previous attacks which occurred within a year before the onset of the empyema in five; in three it occurred two, three, and nine years before respectively. The time was not stated in four. Cough and sputum were present in seven of the thirteen patients. The sputum was examined for bacilli in five, but none were found. Reports of the end-results concerning eight of these patients have been received. Three died. One had a large pneumothorax, and one a persistent drainage and cough and sputum up to the time of death. The empyema was healed in five.

Summarizing the diagnostic findings in the four groups, it may be said that in twenty-three patients the tuberculous nature of the empyema was proved. In thirty-eight others the patient had a tuberculous infection, determined by pulmonary lesions shown in the roentgenogram in twenty-two, and by characteristic histories and symptoms in sixteen, in seven of which the diagnosis of tuberculosis of the pleura was made at operation from gross appearance. Two of the remaining nine patients died of tuberculosis. A presumptive diagnosis of tuberculous empyema was made in these thirty-eight cases. A considerable proportion of the thirteen cases in Group 4 in which there was a history of pleurisy with effusion are probably cases of tuberculous empyema.

The question of the probability of empyema being tuberculous in the presence of a pulmonary lesion is one that cannot be answered categorically. Some writers are of the opinion that they are all cases of tuberculous empyema. The almost constant association of pleuritis, even with early localized pulmonary lesions, is a matter of common observation. It seems obvious that inasmuch as patients with tuberculosis of the lungs develop secondary pyogenic lesions, pneumonia, abscess, and so forth, they may also develop secondary pyogenic pleurisy. The difficulty of proving such cases to be tuberculous empyemas is analogous to the difficulty of establishing positive proof of incipient phthisis. Walton suggests that a distinction should be made between tuberculosis of the pleura, a secondary tuberculosis in a patient with chronic suppurating pleurisy, and suppurating pleurisy in a patient with tuberculosis. From a review of the literature it seems evident that the tuberculous nature of a large proportion of empyemas has remained unrecognized (Table 1).

GROUP 2
CLINICALLY TUBERCULOUS EMPYEMAS

Case.	Sex and age.	Pleurisy.	Illness at onset.	Onset sudden or insidious.	Cough.	<i>Bacillus tuberculosis</i> in sputum.	Rales.	Röntgen-ray findings.	Previous operations.	Operations.	Pathologic diagnosis.	Remarks.
A22339	M. 33	0	"Cold."	I.	+	+	+	Right empyema; tuberculosis of left lung.	1909 Aspiration.	3/23/15 Rib resection for drainage.		Patient left Clinic much improved. Death reported.
A51816	M. 30	+	Pleurisy.	S.	+	+	..	Old pleurisy.		4/19/11 Rib resection for drainage. 12/12/11 Redrainage.		Results unknown.
A121241	M. 4	0	Pneumonia.	S.	+	+	+	Possibly fluid; tuberculosis both sides; thickened pleura.		12/28/14 Rib resection for drainage.		Death one week after discharge from Clinic.
A137779	M. 42	0	"Cold."	I.	+	+	..	Fluid congestion.	6/15 Negative aspiration.	8/7/15 Drainage; empyema necessitatis. 8/16/15 Drainage. 8/28/15 Redrainage.	8/21/15 Chronic inflammation of pleura.	8/28/15 Death. Necropsy; empyema; lung abscess; perforation between bronchus and pleura.
A150774	F. 22	0	Pneumonia.	I.	..	..	+	Thickened pleura.	3 drainage operations.	1/28/16 Drainage.	1/28/16 Chronic inflammation of pleura.	Intermittent drainage; patient's general health fair.
A155183	M. 43	0		I.	..	..	..	Calcified pleura.		3/31/16 Drainage. 10/20/16 Rib resection; redrainage; calcification of pleura.	3/31/16 Inflammation of pleura.	1917 Last report; draining.
A164323	F. 57	+		S.	+	+	..	Probable fluid.	Aspiration.	7/16 Three aspirations. 7/31/16 Rib resection; drainage. 5/4/18 Exploration and redrainage.		Last operation incomplete at patient's request. 3/21 Wound decreasing in size, but not healed.
A167061	M. 53	0	"Cold."	I.	+	+	..	Fluid.	6/16 Aspiration.	7/28/16 Rib resection for drainage.	7/28/16 Exudate negative.	Death two weeks after discharge from the Clinic.
A260196	M. 26	+	Pneumonia.	I.	..	..	..	Retracted ribs; thickened pleura.	5 drainage operations.	2/18/19 Rib resection; skin plastic. 3/18/19 Skin plastic.	3/18/19 Chronic inflammation of pleura.	Wound completely healed; patient developed tuberculosis meningitis. Death 4/20.

CLINICALLY TUBERCULOUS EMPYEMAS—Continued

A284318	M. 42	+	Pleurisy.	I.	0	..	..	Schede operation left; tuberculosis both apices.	3 drainage operations.	4/3/19 Exploration and drainage.		8/8/19 Death.
A288515	F. 31	+		I.	..	..	..	Fluid; ribs resected.	2 drainage operations.	9/16/19 Aspirations, Dakin's solution treat- ment. 9/18/19 Exploration; drainage.	9/18/19 Chronic inflam- mation of pleura.	3/20 Side healed; good health since.
A292083	F. 27	+		I.	+	+	+	Old empyema; pneumo- thorax left lung; thick- ened pleura; tubercu- losis right.	1917 Aspiration.	10/14/19 Aspiration.	10/14/19 Pleural exu- date negative.	Patient sent to sanitarium.
A298385	M. 38	+	Pneumonia.	S.	..	..	..	Congestion left lung; pneumothorax right.	Several aspirations. 1903 Drainage.	12/11/19 Exploration; Dakin's solution treat- ment.		Patient too sick for radical operation; result not known.
A299285	M. 26	+	Pleurisy.	S.	0	0	0	Pneumothorax.	Several aspirations; 2 drainage operations.	1/15/20 Rib resection and skin plastic. 11/9/20 Rib resection and skin plastic.	1/15/20 Chronic inflam- mation of pleura.	7/21 Good health; wound healing rapidly.
A300040	M. 66	..		I.	+	+	+	Fluid left; old empyema right; calcified tuber- culous pleurisy left.		12/24/19 Aspiration.	12/19/19 Pleural exu- date negative.	3/21 Reaccumulation of fluid; further operation not advisable.
A302859	M. 58	+	Pneumonia.	S.	+	+	+	Old empyema, right; large pocket.	1912 Aspiration; drain- age.	1/27/20 Rib resection; drainage. 3/9/20 Rib resection and skin plastic (bron- chial fistula).	1/27/20 Chronic inflam- mation of pleura.	1/21 Wound healed; pa- tient working and in good health.

GROUP 3
EMPHYEMA ASSOCIATED WITH PULMONARY TUBERCULOSIS

Case.	Sex and age.	Pleurisy.	Illness at onset.	Onset sudden or insidious.	Cough.	<i>Bacillus tuberculosis</i> in sputum.	Rales.	Röntgen-ray findings.	Previous operations.	Operations.	Pathologic diagnosis.	Remarks.
A4016	M. 21	0	Pneumonia.	S.	+	+	..	Tuberculosis?		8/2/10 Drainage.		Emphyema healed in 1910. Severe chronic nephritis.
A47069	M. 56	+		..	+	..	..	Tuberculosis opposite side.	Aspiration.	6/20/11 Rib resection; drainage.		Wound had completely healed; patient's general condition much improved at last report. Death, cause unknown.
A70299	F. 20	+	Pleurisy.	S.	..	+	+	Probable fluid; thickened pleura; tuberculosis left lung.	Aspiration negative.	7/29/12 Rib resection for drainage.	7/10/12 Pleural exudate negative.	Sinus healed once; re-opened during pregnancy. 1916 last; report very poor condition.
A73093	M. 19	0	"Cold."	S.	+	..	+	Compression and emphyema with cavity in left lung; tuberculosis both upper lobes.	Aspiration.	9/18/12 Rib resection for drainage.	9/3/12 Mixed infection in pleural exudate.	4/16 Death.
A73419	M. 18	0	Pneumonia.	S.	..	..	..	Fluid left lung; thickened pleura; tuberculosis both upper lobes.	9/10 Drainage.	9/16/12 Rib resection; drainage. 11/27/12 Decortication.		Wound completely healed; general condition good.
A85430	M. 13	+	Pleurisy.	S.	+	+	..	Emphyema right lung; tuberculosis right upper lobe.		7/14/13 Rib resection for drainage. 1/19/14 Redrains.		Health excellent; wound healed soon after second operation.
A87487	M. 42	0	Pneumonia.	L.	+	+	+	Abscess left lung; tuberculosis left lung.		7/15/13 Rib resection for drainage.		Following operation the patient developed parapneumonia of legs. Death within a year.
A87538	M. 46	0	"Cold."	L.	+	+	+	Old tuberculosis and marked density left lung.		7/18/13 Rib resection for drainage (calcareous pleura).		Operation elsewhere for abscess formation. Death 1914.
A120182	M. 19	0	Scarlet fever.	S.	+	+	..	Thickened and retracted pleura; tuberculosis left lung; old emphyema right.	1/14 Drainage.	12/11/14 Drainage. 3/19/15 Rib resection and stern muscle plasty.		Condition fair; permanent healing not secured.

EMPYEMA ASSOCIATED WITH PULMONARY TUBERCULOSIS—Continued

A123274	M. 18	0	Typhoid.	I.	+	..	..	Tuberculosis (?) left lung; old empyema right.	10/14 Drainage. 11/14 Aspiration.	2/3/15 Rib resection and skin muscle plastic.		Complete cure.
A158179	M. 63	0	Trauma.	..	+	+	..	Calcified tuberculous pleura left; fibrosis.	9/16 Drainage.	5/9/16 Drainage.	6/6/16 Guinea pig inoculation negative.	Healing not secured; condition fair.
A165798	M. 57	..	Pneumonia.	S.	+	+	..	Old empyema with collapsed lung left; healed tuberculosis right lung.	1904 Drainage.	7/17/16 Drainage.	7/17/16 Chronic inflammation of pleura.	1920 Death.
A198262	M. 53	+	"Cold."	I.	+	..	..	Empyema with retracted lung, left; tuberculosis (?) right lung.	9/15 Drainage.	6/25/17 Rib resection; drainage.		Results unknown.
A310210	M. 28	0	Gangrenous appendix and subphrenic abscess.	..	..	..	+	Fluid, retracted lung and pneumothorax right; tuberculosis right lung.	4/15 Gangrenous appendix.	10/11/17 Rib resection; drainage. 11/9/20 Exploration. 12/16/20 Rib resection and skin plastic.	10/11/17 Chronic inflammation of pleura.	12/26/20 Death. Immediate cause cardiac failure.
A276632	M. 33	0	Influenza.	S.	..	..	..	Effusion and thickened pleura left; healed tuberculosis right.	10/18 Aspiration. 11/18 Drainage.	7/1/19 Rib resection and skin muscle plastic.	7/1/19 Chronic inflammation of pleura.	Complete cure.
A277537	M. 34	0	Influenza.	S.	+	+	..	Thickened pleura and fluid; tuberculosis left lung.		7/1/19 Rib resection; drainage. 9/29/19 Exploration and Dakin's solution treatment.	7/1/19 Chronic inflammation of pleura.	Complete cure.
A284600	M. 23	+	Pneumonia.	S.	+	+	+	Thickened pleura; healed tuberculosis both lungs.	6/18 Drainage. 11/18 Drainage.	8/16/19 Exploration and Dakin's solution treatment. 11/4/19 Drainage.	11/4/19 Chronic inflammation of pleura.	Cavity still draining; plastic operation probably indicated.
A290735	M. 23	0	Pneumonia.	S.	+	+	..	Thickened pleura.	3/17 Drainage.	10/2/19 Exploration and Dakin's solution treatment. 10/14/19 Drainage.		Wound completely healed.
A301068	M. 27	+	Pneumonia.	..	+	+	..	Tuberculosis of left lung; effusion.	3/18 Drainage.	2/24/20 Exploration and Dakin's solution treatment. 3/4/20 Rib resection and drainage.		Steady improvement.

EMPYEMA ASSOCIATED WITH PULMONARY TUBERCULOSIS—Concluded

Case.	Sex and age.	Pleurisy.	Illness at onset.	Onset sudden or insidious.	Cough.	<i>Bacillus tuberculosis</i> in sputum.	Rales.	Röntgen-ray findings.	Previous operations.	Operations.	Pathologic diagnosis.	Remarks.
A324812	M. 18	+	Influenza; pneumonia?	S	+	+	+	Fluid right; tuberculous both lungs.	3/20 Aspiration.	7/24/20 Exploration and Dakin's solution treatment. 11/19/20 Exploration; drainage.		Patient convalescing.
A341738	M. 18	+	Influenza; pneumonia.	S	+	+	..	Lung collapsed, left; tuberculous with cavity, right lung.	3 aspirations.	11/27/20 Aspiration.	11/23/20 Pleural exudate negative.	Patient to return for probable plastic.
A344044	M. 27	+	Pneumonia; pleurisy.	S	+	+	..	Thickened pleura; tuberculous with cavity, left lung; collapsed right lung.	Aspiration and 3 drainage operations.	12/24/20 Exploration.		Improved; patient to return for a decortication.

GROUP 4
EMPYEMA FOLLOWING IDIOPATHIC PLEURISY WITH EFFUSION

Case.	Sex and age.	Pleurisy.	Illness at onset.	Onset sudden or insidious.	Cough.	<i>Bacillus tuberculosis</i> in sputum.	Rales.	Röntgen-ray findings.	Previous operations.	Operations.	Pathologic diagnosis.	Remarks.
A37110	M. 41	+	Pleurisy.	I.	+	+	..		5 aspirations.	5/20/10 Drainage.		Death.
A39927	F. 25	+	Pleurisy.	S	..	..	+		3 aspirations.	7/7/10 Drainage.		Result unknown.
A40960	M. 32	+	Pleurisy.	S	+	+	..			8/3/10 Rib resection; drainage.	8/3/10. Pleural exudate not tuberculous.	Result unknown.
A42602	M. 4	+	Pleurisy and pneumonia.	S	..	..	..		Drainage.	9/3/10 Rib resection; drainage.		Result unknown.

EMPYEMA FOLLOWING IDIOPATHIC PLEURISY WITH EFFUSION—Continued

A61803	M. 29	+	Pleurisy.	S.	0	..	..	Fluid right.	Drainage.	12/7/11 Drainage. 1/17/13 Redrainage.		1913 Wound healed; patient in good health.
A61968	M. 43	+	Pleurisy and pneumonia.	S.	+	+	..		2 aspirations.	12/9/11 Drainage. 1/3/12 Redrainage. 9/21/12 Redrainage.		Cure.
A117738	M. 53	+	Pleurisy.	I.	+	+	..	Thickened and retracted pleura; drainage in superficial pocket; old empyema left.	4 aspirations; 3 drainages.	12/30/14 Schede; partial decortication.		1915 Death; probably from pneumonia; patient had been doing very well.
A141627	M. 21	+	Pleurisy.	I.	0	0	..	Old empyema of right lung.	9/11 Drainage.	6/2/16 Rib resection and skin muscle plastic.	6/2/16 Chronic inflammation of pleura.	1919 General health excellent; complete cure.
A150376	M. 31	+	Pleurisy.	I.	+	0	..	Left lung collapsed.	10 aspirations; 2 drainages.	9/29/16 Drainage. 8/30/17 Second skin muscle plastic.		9/26/18 Death.
A174822	M. 19	+	Pleurisy.	I.	+	+	+	Fluid right lung.	10/16 Aspiration.	10/11/16 Rib resection and fasciotomy. 6/2/16 Drainage. 11/2/16 Redrainage. 11/29/16 Redrainage. 12/11/16 Rib resection for redrainage.		Complete cure; general health excellent.
A217221	M. 31	+	Pleurisy.	S.	0	..	+	Pleura thickening; pocket base right lung.	Aspiration; 2 drainage operations.	2/16/18 Rib resection; drainage.		Result unknown.
A26109	M. 31	+	Pleurisy.	S.	..	..	..	Retraction, right lung; small pneumothorax.	3 drainage operations.	1/13/20 Skin plastic and fasciotomy. 5/21/20 Skin plastic (grooved fatula). 5/27/20 Small skin plastic.	1/13/20 Chronic inflammation of pleura.	Complete cure; general health very good.
A342864	P. 20	+	Pleurisy; "cold."	I.	+	0	..	Old empyema; lung collapsed, right.	6/20 Thoracotomy.	12/20/20 Rib resection for drainage.		Patient convalescent at last report.

TABLE 1
RELATIVE INCIDENCE OF TUBERCULOUS EMPYEMAS REPORTED

Author.	Cases.	Diagnosis of tuberculosis.	Per cent.
Martin.....	21	3	14.2
Bergeat.....	21	4	19.0
Bythell.....	40	10	25.0
Wilensky.....	82	13	15.8
Moutard-Martin.....	84	7	8.3
Dunlop.....	98	3	3.0
Grieg.....	100	6	6.0
Netter ⁵⁰	109	12	11.0
Hirano.....	118	3	2.5
Voswinckel.....	129	14	10.0
Nathan.....	145	10	6.8
Holsti.....	166	12	7.8
Schede ⁵⁰	484	45	9.3
Hedblom.....	360	61	17.0

A more careful study of cases of chronic empyema in general, of cases in which there is a tuberculous focus, and of cases in which there is a history of a primary pleurisy with effusion will undoubtedly prove a considerably larger proportion to be tuberculous.

TREATMENT

In the treatment of tuberculous effusion, account must be taken of its varied pathology and of the patient's condition. A distinction must first be made between effusion in a closed pleural cavity and one in an open cavity. The exudate in a closed cavity may be sterile or secondarily infected; that in an open cavity is always secondarily infected.

Pleural effusion in a closed cavity.—A sterile effusion in a closed cavity may be serous, hemorrhagic, or purulent. The presence of enough exudate to be clearly recognized clinically is usually considered as an indication for aspirating as much of the fluid as can be obtained. Certainly enough fluid to produce symptoms of mechanical embarrassment to respiration and circulation is generally considered a clear indication for the aspiration of large amounts of fluid. Evidence has been brought forward, however, to show that a sterile exudate exerts a healing effect in a tuberculous process in the lung. Königer reports seventy-eight cases in which marked improvement occurred in all but 3 per cent, and the improvement seemed lasting in more than half. Similar observations have been reported by Mongour, Schröder, Kauf-

mann, Muralt, and others. Spengler and Sauerbruch point out that this does not seem to be due to the mechanic compression of the lung because the improvement observed is not in proportion to the amount of exudate and consequent compression of the lung. They believe the result to be due to a biologic process of great importance. Königer attributes the improvement to a chemical process inducing auto-immunization.

On a somewhat similar basis Gilbert proposed injecting some of the aspirated fluid subcutaneously. Others have since advocated the treatment. Fishberg reports fourteen cases in eleven of which treatment was beneficial, and Lyter reports twenty-three cases with favorable results in eight. When it is considered, however, that the exudate probably contains living tuberculosis bacilli, the rationale of such treatment seems questionable.

From the foregoing it appears very doubtful if it is ever advisable to remove large amounts of fluid at one time. Aside from a possible biologic influence exerted by the fluid its aspiration may exert an unfavorable influence on a coëxisting incipient or active pulmonary lesion. Spengler states that miliary tuberculosis has been known to follow. Clinical experience has also shown that whereas aspirating a large amount of fluid seems to stimulate further exudation, the aspiration of a relatively small amount results in an augmented rate of spontaneous absorption.

In order to prevent reëxpansion of a tuberculous lung, whether by aspiration or rapid spontaneous absorption of the fluid, nitrogen or filtered air may be injected to replace all or a part of the volume of the fluid removed. Such treatment is especially indicated in case effusion follows artificial pneumothorax therapy.

Patients with sterile purulent exudate are of the type most liable to become the victims of injudicious surgery. This condition represents an exception to the rule "*ubi pus ibi evacue*" for the simple reason that there is no pus in the sense of the word used in this hackneyed phrase. A sterile purulent exudate presents essentially the same condition as a serous exudate, and should be treated on the same principles. In many cases in which there are considerable amounts of purulent exudate in the pleural cavity remarkably little evidence of its presence is shown. Baumier reports the case of a young girl who remained well nourished, free from fever, and who worked regularly for three years, although from 1,000 to 1,700 c.c. of pus were aspirated at intervals.

Such patients should not be aspirated indefinitely, however, but an extrapleural plastic operation should be performed. Aside from the danger of a mixed infection either introduced during repeated aspiration or a concurrent infection elsewhere metastasizing to the pleura there is probably in most cases a marked and progressive thickening of the diseased pleura, making the collapse of the cavity by an extrapleural plastic operation more difficult.

A mixed tuberculous and pyogenic infection in a closed cavity, especially with marked sepsis, requires prompt drainage, either by the open or by the closed method, with antiseptic solution drainage. Sterilization by the antiseptic irrigation of the closed cavity has the distinct advantage that the cavity may be considerably reduced in size, and a later extrapleural plastic operation may be performed if a cavity persists. The use of an irritating, and especially of a corroding fluid, such as Dakin's solution, is, however, contraindicated in any case of well marked pulmonary lesion, because of the tendency to bronchial fistula and hemorrhage from the action of the fluid on the exposed diseased area of the parenchyma of the lung.

In mild secondary infections such as pneumococcus it may be possible to treat the case as one of sterile effusion. Spengler recommends irrigation of the pleural cavity with salt solution, 0.5 per cent lysol solution, or a weak solution of iodine and potassium iodide. Jacobsen recommends repeated aspiration in cases of open pleural cavities, with a view to promoting healing of the drainage opening.

Tuberculous exudate in an open pleural cavity.—The opening into the pleural cavity in such cases may be through the chest wall, due to a drainage operation, or to spontaneous perforation of an empyema necessitatis, or into a bronchus due to a ruptured tuberculous cavitation producing spontaneous pneumothorax. These all result in mixed infection.

Cavities following drainage operations vary from those in which there is only a residual tubular or sinus tract to those in which the entire pleural cavity is involved. With cavities of long duration the pleura is usually thickened. Antiseptic solution irrigation in such cases is not only safe, but usually is followed by marked improvement in the patient's general condition. There may be very little thickening of the pleura, however, as in several cases in this series. In one of these symptoms developed suggesting small bronchial fistulas and a lighting up of a tuberculous lesion.

The hypochlorite solution seems to have little or no influence on the tuberculosis bacillus in these cases. Scholl observed a case at the Rockefeller War Demonstration hospital in 1917 in which an empyema cavity of about 500 c.c. capacity was treated with 100 c.c. Dakin's solution every two hours for ten days. Cultures for tuberculosis at the end of that time were positive, showing that the solution did not kill the bacilli.

Small cavities and sinuses seem to constitute favorable cases for the use of bismuth paste. Beck⁵ reports a cure in about 80 per cent of 150 cases of chronic empyema, but he does not state what proportion of these cases were tuberculous. Heuer reports one case in which complete sterilization of a cavity resulted from the use of the paste, so that it was closed as a sterile pneumothorax, but in the case of another cavity the treatment failed.

Cases of impending empyema necessitatis require preliminary open drainage, as a sinus forms if an attempt is made to use the closed method. These cases, often of long standing, as a rule require later plastic operation.

Tuberculous empyema with large bronchial fistula due to rupture of a cavitation into the pleura may result in a virulent secondary infection and require prompt drainage, usually by wide incision, as irrigation with antiseptics is impossible. The immediate mortality in these cases is high. Often patients who survive require later plastic operation. Forlanini had eight patients; all died. Sauerbruch reports seventy-three cases, fifty-seven following pneumothorax therapy, sixteen spontaneous. Fifty-three patients died, most of them soon after drainage operation.

TYPES OF OPERATIONS FOR CHRONIC TUBERCULOUS EMPYEMAS

Drainage operation.—It cannot be overemphasized that the open drainage operation is contraindicated in cases of sterile tuberculous empyema. It will do no good, and is sure to do harm, by introducing a secondary infection. Withdrawal of a part of the fluid by aspiration is indicated in such cases only if the fluid gives rise to mechanical embarrassment. In forty-one patients in this series drainage had been established elsewhere and the cavities were therefore secondarily infected. Of the thirty-five patients who had not had drainage, five belonged to Group 1, in which an absolute diagnosis of tuberculous empyema was made. One of the patients (Case A101014) developed mixed infection following sudden pneumothorax after having been

aspirated several times for serous effusion which contained the bacilli. He died shortly after rib resection. One patient (Case A107204) died of septicemia six days after rib resection. One patient (Case A217107) presented himself with symptoms of an overwhelming infection. He died three days after rib resection for drainage. Necropsy showed extensive tuberculous lesions and the immediate cause of death to be a perforated tuberculous ulcer of the ileum. In the smear made from one patient (Case A149126) the bacilli were found. A rib was resected for drainage. He died six months after operation. The fifth patient had a large seropurulent effusion following exploration for lung abscess. Later examination of the excised pleural tissue showed tuberculosis. The roentgen ray showed a wide-spread tuberculous lesion; the sputum was positive for acid-fast organisms. The empyema cavity healed and the patient improved remarkably, and remained quite well during a period of observation extending over several months.

In seven of the sixteen patients in Group 2 with clinical diagnoses of tuberculous empyema drainage had been instituted elsewhere. On six of the remaining nine rib resections had been performed for drainage, on three (Cases A22359, A51816, and A137779) on account of pyopneumothorax with bronchial fistulas with associated symptoms of mixed infection. One of these patients (Case A137779) also had an impending perforation of empyema necessitatis. Two other patients had large amounts of sputum with marked symptoms of sepsis suggesting possible perforation into a bronchus. One of these two also had an impending empyema necessitatis. A sixth patient had three aspirations followed by prompt reaccumulation of pus. She was considered in too poor condition for a radical plastic operation. A simple drainage operation was performed at the patient's request, and with a view to later plastic operation. Two patients were treated by aspiration only. In one (Case A292083) the pus was sterile and the cavity small. The patient was sent back to the tuberculosis sanitarium from which she came; she died a few months later. The other (Case A300040) was aspirated and the pus was found to be sterile. He did not wish a plastic operation until after trying repeated aspiration. He was therefore recommended to a tuberculosis sanitarium.

Ten of the twenty-two patients with pulmonary tuberculosis and an associated empyema had had previous drainage operations elsewhere. Of the remaining twelve, all except two had rib resection as the primary operation. Pulmonary tuberculosis was present in all of these, but the

general characteristics of the empyema were of the ordinary type. In three repeated aspiration of pus was done, and the culture showed a mixed infection. Cough with a large amount of sputum was present in two, indicating a bronchial fistula. The other patients appeared to have ordinary empyema. In one of these no pus was found, but an empty cavity lined with calcareous deposit.

In Group 4, patients in whom empyema was preceded by idiopathic pleurisy, drainage operation had been performed on eight. Rib resection was performed on the other five.

The closed method in cases of draining cavities secondarily infected is of great advantage if antiseptic solutions can be used. The Dakin's solution treatment was used for ten patients in the first group before the diagnosis had been established. A small bronchial fistula developed in one case during the treatment, but it was not of sufficient size to make it necessary to interrupt the treatment. In one case after a few irrigations it became impossible to use the fluid on account of coughing during which the patient tasted the fluid. He developed fever and increased sputum following the treatment, and lost weight. The treatment was therefore interrupted. This case is an example of a type in which there is only partial incapacity from the presence of the tuberculous empyema, and in which it is questionable if an extensive radical operation should ever be urged. The patient declined to have a Wilm's operation at the time. The antiseptic solution was relatively harmless in this case, and of great advantage in all of the other cases, since the symptoms referable to septic absorption were distinctly ameliorated.

Decortication of the lung by the Delorme-Fowler method.—It seems questionable whether this operation is ever indicated in the presence of an extensive or active phthisis. In such cases fibrosis limiting the expansibility of the lung and the danger of lighting up a latent focus must always be considered. In other cases without a demonstrable pulmonary lesion it is impossible to separate the thickened membrane from the lung. Delorme writes that tuberculous empyema is not a contraindication to the operation. The most favorable report found in the literature is by Violet, who reported seventeen cases in which the operation succeeded in ten and failed in seven. Tuffier states that cases in which it is difficult or impossible to liberate the lung are as a rule tuberculous.

In the present series of seventy-four cases decortication was attempted in six, in all before the tuberculous nature of the empyema

had been recognized. These cases have been reported elsewhere.²³ In five the cavity seemed materially reduced at the later operation, but it is questionable whether sufficiently so to warrant the operation. In all these cases a later plastic operation was required. In one of these (Group 1, Case A263092), in which there was no demonstrable lesion in the lung, the pleura was only very little thickened, but the surface of the lung was very irregular and corrugated, making decortication impossible, although the lung was freed up *en masse*. In one case (Group 1, Case A289416) the surface was smooth, but the pleura was thickened over the upper portion of the lung only, thinning down to normal proportions toward the base. In the other cases there was nothing about the appearance of the pleura to suggest the tuberculous condition shown by microscopic examination. In one case (Group 3, Case A73419) the cavity was completely obliterated.

Plastic operations.—The Estlander extrapleural rib resection, complete resection of the whole thickness of the chest wall with the use of a skin flap (Beck⁴), a skin muscle flap following a similar resection (Robinson), extensive radical resection (Schede⁶⁷), and the extrapleural two-stage or three-stage rib resection of Wilms have all been used with success in the treatment of tuberculous empyema. Beck's operation, which is similar in principle to the Schede operation, lends itself well to the treatment of relatively small residual cavities following rib resection for drainage. For large infected cavities the Schede operation best meets the anatomic indications, but the mortality of the one-stage operation has been as high as from 70 to 80 per cent (Spengler and Sauerbruch, Wilms).

In cases with cavities of large size, often with an associated pulmonary lesion and usually with marked debility, a several-stage extrapleural rib resection not only gives a low mortality, but offers good prospect of cure. This operation is an outgrowth of an attempt to modify the Estlander operation. Jaboulay and Lemaire, instead of performing an Estlander resection of the ribs over the whole extent of the cavity, simply cut the ribs on the sternal border; Boiffin sectioned them at the vertebral border of the cavity. Tietze later combined the two methods and Wilms modified it by resecting segments several centimeters long, chiefly posteriorly, but also anteriorly, if necessary, and dividing the operation into two or three stages. Freidrick proposed to call the procedure the Boiffin-Wilms operation. Wilms calls it the Pfeiler resection, and first used the method for collapsing the

chest wall in cases of uncomplicated pulmonary tuberculosis. Kolb and, later, Wilms and others applied the method to tuberculous empyema.

Wilms recommends resecting 10 or 15 cm. of the sixth to the eleventh ribs posteriorly at the first operation, and 8 to 10 cm. of the fifth to the second or first ribs, with suturing of the wound at a second operation.



FIG. 259 (Case A185290).—Overriding and fusion of the ribs in tuberculous empyema of twenty-two years' duration.

This permits the entire chest wall to sink in, the elasticity of the sternal ends of the ribs allowing considerable mobility. Only if further collapse is necessary are the sternal ends of the ribs sectioned. If a cavity still persists a flap can be turned back and the rib segments and the portion of the pleura overlying it can be excised. The operation can be performed under local anesthesia; it results in but slight trauma

to the tissues; the posterior incision is a safe approach to the second and to the first ribs. The operation in stages and the freedom from infection in the wounds makes it relatively safe for very poor surgical risks. The advantages of the operation are almost equally great in cases in which there is mixed or secondary infection, but in these there is a characteristic tendency to a persistent sinus. Wilms reports twelve



FIG. 260 (Case A185290).—Visceral aspect of specimen shown in Figure 259. Note thickness of parietal pleura.

cases without mortality, and other successful cases following this operation are reported by Linderström.

In the series of seventy-four cases plastic operations were performed in twelve cases in Group 1 (Figs. 259 and 260), in three cases in Group 2, in four cases in Group 3, and in three cases in Group 4. In Group 1 Beck's operation was performed as a preliminary operation in three,

and as a secondary operation in nine. An operation of the Schede type was performed in five, in one for a draining empyema of twenty-two years' duration, and a Wilms operation in three stages was performed in one. That a Schede operation is the only operation that will obliterate the cavity in some instances was obvious in the case of the empyema of two years' standing. The ribs were overriding and so much thickened that it was impossible to separate them for resection. The pleura, moreover, was fully 2.5 cm. thick and very rigid. In such a case very little would probably be gained by any procedure that would not include eventually a complete resection of the enormously thickened, chronically diseased chest wall.

Resection of the scapula is sometimes desirable in plastic operations. Hellström believes that it should be performed in all cases.

RESULTS OF TREATMENT

The type and sequence of the operative treatment at the Mayo Clinic is indicated in Tables 2 and 3. In these tables insertion of a tube for aspiration and Dakin's solution irrigation is listed as aspiration. Drainage operations were for the most part rib resections. It will be noted that the decortication was performed with one exception as a primary operation. In these cases the diagnosis of the tuberculous nature of the empyema was made from the excised pleura. Plastic resections were, as a rule, secondary procedures. The results grouped according to the operations are shown in Table 4.

The patients who had several operations are grouped under the heading of the last operation or under the operation which is judged to have contributed most to the result obtained. It will be noted

TABLE 2
TYPES OF OPERATION (MAYO CLINIC SERIES)

	Aspiration.	Exploration.	Drainage.	Decortication.	Skin plastic.	Skin muscle plastic.	Schede's operation.	Wilms' operation.	Total.
Group 1...	13	5	16	5	5	4	4	3	55
Group 2...	6	4	13	..	5	..	..	..	28
Group 3...	1	8	18	1	1	3	..	..	32
Group 4...	..	1	17	..	3	2	1	..	24
Total...	20	18	64	6	14	9	5	3	139

TABLE 3
SEQUENCE OF OPERATIVE PROCEDURE (MAYO CLINIC SERIES)

Type of operation.	First operation.	Second operation.	Third operation.	Fourth operation.	Total.
Aspiration.....	17	1	2	..	20
Exploration.....	11	5	2	..	18
Drainage.....	41	17	4	2	64
Decortication.....	5	1	..	..	6
Skin plastic.....	4	8	2	..	14
Skin muscle plastic.....	4	4	1	..	9
Schede.....	2	2	1	..	5
Wilms.....	..	1	1	1	3
Total.....	84	39	13	3	139

TABLE 4
RESULTS BY OPERATION

Operation.	Cure.	Good health, sinus.	Im-prove-ment.	No im-prove-ment.	Opera-tive death.	Death later.	Total deaths.	Un-known.	Total.
Aspiration.....	..	..	1	1	..	1	1	..	3
Exploration.....	..	..	..	..	1	1	2	1	3
Drainage.....	9	5	8	2	7	9	16	6	46
Decortication.....	1	..	..	..	..	..	..	..	1
Skin plastic.....	3	2	..	..	1	3	4	..	9
Skin muscle plastic..	3	2	3	..	..	..	..	..	8
Schede.....	..	1	..	..	1	1	2	..	3
Wilms.....	..	1	..	..	..	..	..	..	1
Total.....	16	11	12	3	10	15	25	7	74

that the largest proportion of cures followed plastic operations. The high mortality in the group in which a drainage operation only was performed is owing to the relatively poor condition of these patients.

The results are grouped according to the pathologic subdivisions in Table 5. It will be noted from this table that of sixty-seven patients

TABLE 5
RESULTS BY GROUPS

	Cure.	Good health, sinus.	Im-prove-ment.	No im-prove-ment.	Opera-tive death.	Death later.	Total deaths.	Un-known.	Total.
Group 1...	2	7	5	..	5	4	9	..	23
Group 2...	2	3	2	..	3	4	7	2	16
Group 3...	7	1	4	3	1	5	6	1	22
Group 4...	5	..	1	..	1	2	3	4	13
Total...	16	11	12	3	10	15	25	7	74

in whom the end results are known about 58.2 per cent were cured, or much improved, 4.5 per cent were not improved, and 37.3 per cent died. The postoperative mortality, deaths within two months of operation, was 14.9 per cent.

Of the patients in Group 1, definitely proved to be tuberculous, 61 per cent were cured or greatly improved; 39 per cent died. The postoperative mortality was 21.7 per cent. In Group 2, patients with clinically tuberculous empyema, the results are known concerning fourteen; 50 per cent were cured or much improved and 50 per cent died. The operative mortality was 21.4 per cent. In Group 3, patients with empyema associated with pulmonary tuberculosis, 57.1 per cent were cured or much improved, 14.3 per cent not improved, and 28.6 per cent died. The postoperative mortality was 4.7 per cent. In Group 4, patients with empyema following pleurisy with effusion, 66.6 per cent were cured or improved; 33.3 per cent died. The postoperative mortality was 11 per cent.

SUMMARY

1. Primary or idiopathic pleurisy with effusion, in a large proportion of cases, is probably tuberculous in nature.

2. A past history of pleurisy with effusion is common in cases of tuberculous empyema. In many cases the effusion is serous at the onset.

3. Tuberculous pleurisy may be primary, or it may be secondary to a pulmonary, peritoneal, or other tuberculous lesion.

4. The onset of a tuberculous effusion may be insidious or it may be sudden and associated with an acute and severe constitutional reaction.

A mixed pleural infection due to the perforation of a tuberculous cavity often runs an acute and rapidly fatal course.

5. Diagnosis of tuberculous empyema is made by demonstration of the bacilli in the exudate, by animal inoculation, or by examination of the sectioned pleura.

6. A sterile effusion is probably tuberculous. An infected effusion may be tuberculous.

7. Empyema following primary idiopathic pleurisy with effusion, or empyema of insidious onset, especially in the presence of a pulmonary or other tuberculous condition, is probably tuberculous.

8. Empyema may be tuberculous in spite of persistently negative findings over a long period of time.

9. In a closed pleural cavity a sterile effusion, whether serous or purulent, should not be treated by open drainage, except in the presence of an impending perforation of the chest wall.

10. Repeated aspiration of only part of the fluid present is indicated in cases of serous effusion producing definite dyspnea on exertion or symptoms of circulatory embarrassment.

11. The replacing of aspirated fluid by nitrogen or filtered air may be indicated in cases in which there are symptoms of active phthisis referable to the same side as the effusion.

12. A sterile purulent effusion should be treated as though it were serous if the lung expands when fluid is withdrawn. If the lung is fixed in a collapsed condition or if the effusion persistently recurs, an extra-pleural plastic operation is indicated.

13. Effusion in a closed cavity showing a mixed infection should be treated by the closed method with antiseptic solution irrigation, or by open drainage; the open drainage is indicated especially in cases of severe infection associated with extensive pulmonary tuberculosis, making irrigation hazardous.

14. Tuberculous empyema with a large bronchial fistula should be drained by the open method.

15. A large tuberculous empyema with mixed infection from a previous drainage operation or from spontaneous perforation of the chest wall requires a plastic operation, preferably after treatment with Dakin's solution.

16. A plastic operation involving closure of a bronchus offers the only prospect of cure in case of an associated large bronchial fistula.

17. Dakin's solution irrigation may be contraindicated in the

presence of an extensively diseased lung, owing to its corroding action on any superficial lesion, possibly resulting in hemorrhage or the formation of a bronchial fistula.

18. A plastic operation is usually eventually required in the case of closed cavities when the empyema is of long standing, and of all large open secondarily infected cavities.

19. An extrapleural rib resection is indicated for the collapse of closed sterile cavities. The Boiffin-Wilms operation is especially suitable for the collapse of large cavities without excessive thickening of the parietal pleura or rib deformity.

20. A skin or skin muscle plastic is indicated for the obliteration of relatively small cavities. Cases of long standing associated with greatly thickened pleura require an extensive resection of the entire chest wall after the method of Schede.

21. Operation in several stages is especially indicated in the treatment of tuberculous empyema, and, if practicable, it should be preceded by antiseptic solution irrigation. Such treatment should extend the indications for operation and should lower the postoperative mortality.

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THE TREATMENT OF PERICARDITIS WITH EFFUSION*

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Pericarditis is an inflammation of the serous layer of the pericardium. The inflammatory process, however, often extends outward though the whole thickness of the pericardium, involving adjacent structures, and inward into the musculature of the heart.

Inflammatory exudation presupposes infection which, with rare exceptions, is probably always present. A hemorrhagic effusion may be due to malignant disease. Pericarditis has been observed following the injection of diphtheria antitoxin (Cunnington), and recently a case of hemorrhagic pericardial effusion following arsphenamin injection, but probably due to malignancy, has been observed in the Mayo Clinic. Wachter, Vergely, and others have reported cases of syphilitic pericarditis.

The older writers recognized primary idiopathic pericarditis following chill or trauma, a condition analogous to the so-called primary idiopathic pleuritis with effusion. It is now quite generally accepted, however, that in the great majority of instances this type of pleurisy is tuberculous. McPhedran believes that a considerable proportion of cases of plastic pericarditis are tuberculous. It seems probable that also many of the cases of pericarditis with effusion are tuberculous.

The occurrence of a tuberculous pericarditis when there is no tuberculous focus elsewhere, pulmonary, pleural, or glandular, has been questioned, and by some writers categorically denied. To vouch for the occurrence of such a primary lesion, however, is no less an authority than Virchow, who describes a case in detail in which careful search at necropsy failed to demonstrate any lesion whatsoever outside the pericardium. Similar cases have been reported by Thym, Meltzer, Scagliosi, Jahn, and Fromberg.

The most frequent cause of primary pericarditis is probably the infective organism of acute articular rheumatism, which in such cases

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attacks the serous layer of the pericardium rather than that of a joint. Cases have been observed in which a friction rub was the first sign of an acute articular polyarthritis.

Pericarditis is usually secondary to a disease process elsewhere. Acute articular rheumatism is the most frequent primary disease entity. Pleurisy and pneumonia, the acute general infections, tuberculosis, and syphilis represent the less frequent associated disease conditions. In a series of 100 cases at the Boston City Hospital during fourteen years, Sears found the pericarditis associated with acute rheumatism in fifty-one, with pneumonia and pneumococcus infection elsewhere in eighteen chronic nephritis in seven, pleurisy in five, gonorrhea in two, chronic rheumatism in two, and in one case each with empyema, tonsillar abscess, acute nephritis, hepatic cirrhosis, and chronic fibrous pneumonia. Nine cases were classified as idiopathic.

In young children and infants suppurative pericarditis seems to be largely a complication of pleurisy and pneumonia. Of 100 cases reported by Poynton sixty occurred in association with empyema and forty with pneumonia.

Clinically pericarditis with effusion is usually classified as serous, hemorrhagic, or purulent, or as combinations of these types of exudates. In Sears' series "fifty-four were dry, forty-one serous, four hemorrhagic, and five purulent." Of 100 cases that have come to necropsy at the Mayo Clinic since 1910, twenty-three were acute fibrous, twenty adhesive or obliterative, twenty-seven serous, twenty-one purulent, and four hemorrhagic. This classification, however, has no etiologic basis. In rheumatism the exudate is usually serous, but may be hemorrhagic or purulent. The effusion is most liable to be purulent in association with suppurative pulmonary and pleural processes, especially those due to the epidemic type of streptococcus infection. McPhedran states that a purulent effusion is usually such from the onset. Hemorrhagic effusions are especially frequent in association with purpura, scorbutus, and malignant disease, but also with tuberculosis, nephritis, and the cachectic states.

DIAGNOSIS

Diagnosis is of prime importance in any consideration of pericarditis. McPhedran states that no acute disease is so frequently overlooked. An adequate discussion of the diagnosis is beyond the scope of this paper. In general it may be said that diagnosis of the presence of a

pericardial effusion is based on finding a pericardial friction rub, which may or may not disappear, increased precardiac dullness, and enlarged heart shadow on roentgen-ray examination, feeble or absent heart sounds, absent apex impulse, small rapid pulse, dyspnea, and cyanosis. Occasional signs are dysphagia, precardiac pain, pulsus paradoxus, and recurrent nerve paralysis. Downward displacement of the liver and dullness in the left side of the back may also be found. The differential diagnosis is essentially between pericarditis with effusion and cardiac dilatation.

SURGICAL TREATMENT

The principles of the surgical treatment have been developed through the cumulative experience of many surgeons. No large series of original cases has been reported. The relatively small individual surgical experience is pointed out by Kolb. He states that at the Heidelberg Clinic, from 1897 to 1911, 30,050 operations were performed. Among these were one pericardiocentesis, four pericardiotomies, and four cases of cardiolysis. Whittemore writes that the records of the Massachusetts General Hospital contain the histories of only two operations for purulent pericarditis.

From the standpoint of surgical treatment the important consideration is the presence or absence of living pyogenic or tuberculosis bacilli in the exudate. What the specific infective organism may be, whether the streptococcus, staphylococcus, pneumococcus, Friedlander's bacillus, *Bacillus coli*, *Bacillus pyocyaneus*, or the gonococcus, is of significance chiefly with reference to prognosis. The treatment is drainage. A sterile or tuberculous exudate in general may require evacuation, but never by open drainage.

Pericardiocentesis.—Pericardiocentesis is indicated in all cases of suspected effusion in order to establish the diagnosis and to evacuate a sterile exudate in case it is causing embarrassment to the circulation. As a diagnostic procedure it may serve both to establish the presence of fluid and to determine its nature. Negative aspiration, however, does not exclude the presence of an effusion, as emphasized by Jacob.³⁸ A purulent exudate in the presence of fever, leukocytosis, and other findings characteristic of a suppurative process may be assumed without further investigation to be infected, and open drainage should be instituted at once. If the symptoms pointing to a pyogenic infection are less definite and the fluid proves to be turbid, a culture or direct

examination may be necessary in order to establish the presence of living pyogenic organisms. Rarely a tuberculous effusion is frankly purulent and may occur with fever, night sweats, and so forth, suggesting a pyogenic origin. In such cases a sterile culture and a predominance of lymphocytes in a stained smear justify a tentative diagnosis of tuberculous pericarditis; open drainage would almost certainly lead to a secondary pyogenic infection and greatly lessen the patient's chances for recovery.

In cases with large effusion and in many cases with signs of only a very moderate effusion, symptoms of dyspnea, cyanosis, feeble pulse, distention of the veins in the neck, coldness of the extremities, edema, and, in some cases, marked pain, are associated. Some writers attribute these symptoms to cardiac weakness and not to the mechanical effect of the pericardial fluid. McPhedran believes "the danger from pericarditis is rarely due to the inflammation of the serous membrane itself, but first to the presence of the accumulated effusion hampering the action of the heart, only an occasional danger, and secondly and chiefly, to the occurrence of inflammation in the walls of the heart itself." That the symptoms in these cases may be largely due to increased intrapericardial pressure is, however, abundantly appreciated by anyone who has seen the immediate relief from pericardiocentesis to a practically moribund patient. In such cases it is life saving.

The reason why a large pericardial exudate or even a rapidly accumulated smaller one may seriously embarrass the return of the blood to the heart becomes clear when it is considered that normally the negative intrathoracic pressure of from 0.3 to 30 mm. mercury (Starling) is transmitted through the pericardium, so that the intrapericardial pressure is normally -3 to -5 mm. mercury (Adamkiewitsch and Jacobson). In the presence of a pericardial exudate, owing to the rigid pericardial walls limiting the pressure on the lungs, the intrapleural pressure usually remains but slightly if at all affected. Inside the pericardium, however, I have found that the pressure varied in one case between 6 and 20 cm. of water. A few such observations are also recorded in the literature. Riechard has recorded a pressure of 15 cm. water, Gerhardt, 24 cm., and Hanssen 17 cm. In one of Gluck's cases 250 c.c. of blood sufficed to "strangulate" the heart.

Experimentally it has also been shown by François-Franck, Lagrolet, Kuno, and others that in animals a relatively small amount of fluid in the pericardium causes a diminution in the output from the heart,

resulting in increased pulse rate. Further increase in pressure causes a fall in blood pressure. Finally, when the intracardial pressure reaches the pressure in the venæ cavæ and auricles the heart stops. A striking analogy is found in the increased pulse rate, lowered pulse volume, and blood pressure and increasing dyspnea and cyanosis in cases of large rapidly accumulating pericardial effusion.

The site for pericardiocentesis.—There have been much discussion and diversity of opinion on the proper site for pericardiocentesis. Doebert objects that in textbooks sufficient consideration to the subject is not given; in many it is not even mentioned. It is of practical importance chiefly, perhaps, with reference to finding the bulk of exudate in case aspiration of the fluid is attempted therapeutically, and because of the danger of wounding the heart or mammary vessels and the risk of infecting the pleural cavity if a pyogenic bacterial exudate is present and the puncture is made through the pleura.

The position of the heart in the presence of an exudate is of first importance because of the chance of injuring it and the location of the exudate. The old conception first expressed by Scoda and later by many others (Niemeyer, Schrötter, Potain, Trousseau) was that the heart, being of greater specific gravity than the exudate, sinks backward when the patient lies in the dorsal position. According to this conception there would scarcely be any danger of injury to the heart in the presence of a large exudate by inserting the needle near the sternal edge where the pleura and the mammary vessels are avoided; nor would there be any failure to aspirate the exudate. Clinical experience has shown, however, that it may be impossible to obtain fluid by aspirating at the sternal edge even in the presence of a large exudate, and often the heart has been punctured and blood aspirated, in a few recorded cases with fatal result (Mignon, Calander, Baizeau, Southey, and others). Gluck believes that puncture of the heart may be dangerous in the presence of a degenerated heart and says he has observed two fatal cases. Delorme and Mignon and Fränkel believe that the chief danger is wounding the large dilated coronary vein lying in the left longitudinal sinus.

The failure to obtain fluid and the occasional accidental puncture of the heart during aspiration suggested an anterior position of the heart and led to experimentation on the cadaver to determine its position, after injection with plaster of Paris, cocoa butter, gelatin, agar, and so forth, into the pericardial cavity. Such experiments were per-

formed by Goodle, Ferrand, Rotch, Schaposchnikoff, and Damsch, and recently by Williamson. It was found that the heart does not drop back, even when the specific gravity of the fluid is less than that of the pericardial exudate, but that the bulk of the infected material lies below, laterally and posteriorly to the heart. In some instances there is a thin layer of fluid in front of the heart, in others none. The same findings were noted by Rehn at necropsy in a fatal case of hemopericardium. Gluck writes that the heart lies anteriorly like the patella. He cites a case in which even after pericardiotomy no exudate was obtained until the finger was inserted laterally between the heart and the pericardium. Curschmann points out that the backward dislocation of the heart against the posterior chest wall is impossible on account of its fixation through the great vessels. It must be borne in mind, however, that the anatomic relations may be distorted by a large effusion. Meyer has recorded a case in which the heart at pericardiotomy lay beyond reach of the finger. Fränkel and Brentano⁸ also have noted at operation that the heart lies anteriorly. I have also felt the heart beat against the needle in a number of cases; in one such case after evacuation of the fluid the heart could scarcely be reached by the examining finger.

The experiments cited above also bear out the clinical observations that the bulk of the fluid accessible to aspiration usually lies below or to the left, but may be on the right of the heart.

The internal mammary vessels are said to lie from 0.5 to 2 cm. from the sternal border (Gray, Piersol, Delorme and Mignon).

In spite of these observations there is a diversity of opinion on the most suitable position for aspiration. Some surgeons consider the danger of injury to the heart, others the danger of contaminating the pleura, to be the greatest evil. Kocher,⁴¹ Strümpell, and Delorme and Mignon recommend aspiration at the sternal edge; Dieulafoy 6 cm. outside the sternal edge, that is, outside the mammary vessels, and Gluck and West outside the mammary line; Curschmann and Damsch state that the aspiration should be performed at the point where the findings indicate the greatest amount of fluid. Fränkel²⁵ has reported two cases, Schaposchnikoff four cases, and Doeberst one case in which aspiration to the right of the sternum was successful (Roberts). Roberts and Marfan advise aspiration in the costoxiphoid angle. Hoffmann advises aspiration from behind, in certain cases, piercing the lung. Others, among them Lundmark, Brentano,⁹ Mosse, Strümpell,

Gluck, and Sjövall and Tallqvist, express a preference for a primary pericardiotomy as being less dangerous and more certain of securing adequate evacuation. Kolb believes that in case of negative aspiration open operation is indicated. Souligoux reserves aspiration for hydropericardium.

The great variation of opinion as to the proper site for puncture seems to indicate that all sites have their shortcomings. Rehn remarks that the more numerous the methods, the more sparingly should any of them be used. A very important consideration and one which has a bearing on the whole question is the technic and the needle used for the aspiration. If a large needle or a trocar is used, as seems to have been the rule, it is a matter of considerable importance where and how many times it is inserted. The injury to the heart and mammary vessels may be of grave consequence, and the chances of contamination of the pleura may be considerable. The introduction of the needle without good regional anesthesia is an ordeal for a sick patient. If, on the other hand, a short hypodermic needle is used following local anesthesia, the procedure becomes practically painless and harmless, so that if fluid is not obtained at the point where it would seem most likely to be, further exploration can be done. I have repeatedly aspirated several hundred cubic centimeters of exudate, serous, hemorrhagic, and frankly purulent, through a hypodermic needle 4.5 cm. long without the slightest ill effect on the patient. I have also felt the heart beat against the needle in cases with effusion and in cases without effusion, and in one instance aspirated blood, apparently from the auricle, without the least effect on the patient. I submit this technic as one in which the chance of serious harm is negligible, compared with the advantage of a positive proof of pericardial effusion.

Many surgeons caution against too rapid withdrawal of a large effusion. Curschmann employs gravity aspiration. According to his views, aspiration evacuates the fluid too rapidly and may produce shock and cardiac collapse. Kolb and Küttner also recommend very gradual evacuation, and advise against aspiration. Others, on the contrary, use some form of aspiration. On *a priori* grounds it seems illogical to fear bad results from too rapid evacuation in cases of serous effusion, which is usually treated by aspiration, when purulent exudates, with which probably a greatly more frequent and severe myocardial weakness is associated, are drained by wide incision in the pericardium. On two occasions I have emptied an exudation of about 2 l., in one

case by aspiration, in the other by open incision with the patient under local anesthesia, and with frequent observation of the blood pressure and pulse rate. At no time was there the slightest indication of an untoward effect. In other cases the fluid has been aspirated with a 20 c.c. syringe without any untoward symptoms attributable to the aspiration.

The question of repeated aspirations arises in case of reaccumulation of a sterile exudate. In most cases the effusion ceases and the remaining exudate is absorbed after varying intervals, due, according to McPhedran, to a restoration of the permeability of the vessels. In some cases, however, notably in tuberculous and hemorrhagic pericarditis, the effusion reaccumulates. McPhedran cites a case in which aspiration was performed thirteen times, but the patient died. In one case at the Mayo Clinic on the service of Dr. Willius I aspirated a hemorrhagic effusion thirteen times. In another case, tuberculous pericarditis, aspiration had been performed three times elsewhere.

In these cases of recurrent effusion injection of air into the pericardium and also open drainage have been advocated. Wenckebach and Weil and Loiseleur report cases cured by this treatment. Alexander recommends air injection to prevent adhesive pericarditis.

Pericardiotomy.—Pericardiotomy with drainage is indicated in cases of nontuberculous purulent effusion. It was demonstrated very early that aspiration is absolutely inefficient. In the nine cases reported before 1889, in which the treatment was aspiration, all the patients died (Fevrier). The operation is also indicated to establish the diagnosis in cases in which exploratory aspiration has failed, but if the needle is inserted laterally, on both sides if necessary, or if insertion there fails, enough fluid will probably nearly always be obtained from below to establish the diagnosis. Pericardiotomy is also urgently indicated in cases with large effusion embarrassing the heart in which aspiration fails to evacuate a sufficient amount of fluid to relieve the pressure. There may be trabeculated cavitations in such cases. The open operation has been advocated as a primary procedure also for sterile serous exudates, notably by Küttner, Lundmark, Rochard, and others. Rochard writes that precardiac puncture is diagnostically untrustworthy, dangerous, and therapeutically inefficient.

Pericardiotomy with drainage would seem always to be a questionable procedure in cases of sterile exudation, even though purulent, as in the case of tuberculous effusion, on account of the probability of

infection. It has been argued that in cases of tuberculous effusion open operation with closure might result in an improvement similar to that following laparotomy for tuberculous peritonitis. That in such cases open drainage is followed by unfavorable results, however, as it is following laparotomy for tuberculous peritonitis, is indicated by the fact that recovery was reported in only one of the cases collected by Berteaux. Favorable results following drainage of sterile effusions have been reported, however, by Meyer and by Dowd. Pericardiotomy without drainage performed at the Mayo Clinic in one case with 2,000 c.c. of tuberculous exudate was followed by marked general improvement, but gradual reaccumulation of the exudate. At a second pericardiotomy in this case drainage into the subcutaneous tissues was attempted after the method described by Jacob.³⁹ Sufficient time has not elapsed in this case to determine the ultimate results, but the indications are favorable.

The technic of pericardiotomy.—In selecting the site for incision and drainage the choice is distinctly more limited than for pericardiocentesis. These limitations are the reflections of the pleuræ, the anterior edges of the lungs, and the sternum. The pleural reflections are parallel and run close together behind the sternum from the level of the first rib to about the level of the fourth; the left pleural reflection then deviates somewhat and in variable amounts to the left, leaving a small area behind the fifth, sixth, and seventh ribs bare of pleura. The average point of crossing measured from the sternal edge, according to Luschka, is 1.5 cm. at the fifth rib, 2 cm. at the sixth, and 2.5 cm. at the seventh. Considerable anatomic variations occur, however; Lundmark, in a study of twenty cadavers, found that the pleural reflections in three continued parallel all the way down, in one behind the sternum, in one behind the right sternal edge, and in another behind the left sternal edge. Sick, studying the pleural relations in twenty-three adults, found that the pleural reflection at the level of the cartilage of the fifth rib lay at or within the left border of the sternum in seventeen; at the level of the sixth cartilage the pleural border had not gone beyond the sternal border in ten; at the level of the sternal articulation of the seventh cartilage it was at the sternal border in nine or this cartilage was below its lower border. In eight of twelve children the pleural reflection was at the sternal border at the level of the sixth cartilage. Dwight, Delorme and Mignon, and others essentially agree. Rehn attributes many deaths to opening the pleura. He believes that

the ideal method is to operate in a differential pressure chamber. In the presence of pleural effusion the tendency is, however, for the lungs to be crowded back, and in the presence of a purulent exudation the pleural surfaces are probably usually adherent, effectively walling off the pleural cavity. In pericardiotomy the mammary vessels may either be retracted outward or ligated and cut.

Except perhaps in children the operation should be performed under local anesthesia; it is important to remember that anteriorly the intercostal nerves run midway between the cartilages. The pericardium does not appear especially sensitive. On five occasions while operating under local anesthesia without infiltration of the pericardium I have incised it. Harrigan reports a case, however, in which the heart stopped beating when the pericardium was incised with the patient under ether-oxygen anesthesia. Heitler and d'Agata, on an experimental basis, recommend cocainizing the pericardium before incising it. Patients who are dyspneic, and especially if cyanosed and with a rapid weak pulse, should be operated on in bed, and every effort made to minimize their discomfort and excitement.

Numerous variations in the type of incision and the position and number of cartilages or ribs resected have been described and recommended. Reichard resects the third and fourth cartilages, Ollier, Gussenbauer,³² and Durand the fifth, Axhausen, Kocher,⁴² Pels-Leusden, the sixth, Delorme and Mignon the fifth and sixth, Lorey, Mintz, and Rehn the seventh. Bérard and Péhu have devised a transxiphisternal route, dissecting the sternum from the diaphragm. Roberts proposes an osteoplastic flap, and Gluck resects the fifth and sixth ribs laterally. Romberg advises rib resection and drainage to the right of the sternum in cases in which the exudate lies to the right. In my experience, resection of the fifth and sixth cartilages has given adequate and dependent drainage. I have found knife section of the cartilage to be less hazardous to the underlying structures than the use of forceps. von Eiselsberg, Brentano, and Gussenbauer³³ suture the pericardium to the muscle or wound edges in order to protect the pleura. The important considerations in the approach are to avoid opening the pleural cavity and to secure dependent drainage.

The matter of efficient drainage is one of the greatest importance. The presence of recesses in the pericardial cavity on either side of the venæ cavæ behind the heart, into which the exudate gravitates with the patient in a dorsal position, is the worst possible combination for

drainage. When it is further considered that the heart tends to assume a forward position, as I have repeatedly observed, and to form adhesions anteriorly, it is easy to understand how the pus may be encapsulated behind it. Many patients who do well for a time, but who die later, probably succumb because of failure to maintain adequate drainage of these most dependent parts. Kolb and Rehn recommend long tube drainage, one tube passing behind the heart to the right over the inferior vena cava, the other to the left. A reclining posture of the patient has in my experience not seemed sufficient materially to improve the drainage, and it is probably as a rule impractical to have the patient lying face downward.

On account of the difficulty with drainage the cavity has been irrigated with saline solution and with various antiseptics, such as thymol, phenol, and lysol. Kocher⁴³ warns against antiseptics and Küttner uses sterile water. I have used Dakin's solution in two cases of severe hemolytic streptococcus infections. In both of these death occurred from generalized septicemia. It seems noteworthy, however, that one of these patients lived several weeks following drainage of a large bilateral empyema and purulent pericarditis, and with a biliary fistula into the pericardial cavity. He died from a hemorrhage into the pleural cavity, probably from the corroding action of the solution on a subpleural abscess cavity, such as was often observed in similar cases during the hemolytic streptococcus epidemic.

An original method of drainage recently described by Whittemore consists in inserting a catheter by means of a trocar and cannula into the pericardial cavity, directing it backward from the left around the heart to the posterior recess. The pus is aspirated, but no irrigation used. His patient, who had a purulent pneumococcic pericarditis, with double otitis media as a complication, made a good recovery. Possibly this method, combined with Dakin's solution irrigation, may prove to be safe and practical. My preference, however, would be to combine the irrigation with open drainage. Pneumothorax is not a factor in the drainage of pericarditis with effusion.

RESULTS

Venus, in a series of 178 collected cases treated by aspiration, intercostal incision, or rib resection, found the combined mortality to be 56.18 per cent. Ninety-three patients were treated by aspiration; many of these, however, had suppuration from the earlier period before

open drainage had been instituted; all of these died. Of ninety-three patients treated by aspiration 62.37 per cent died, 31.18 per cent recovered, and 6.45 per cent were improved. Venus ascribed only one death to the operation. Many of the patients were moribund at the time of operation, and many of these made a temporary recovery. Intercostal incision for drainage was performed in forty-nine, with a mortality of 53 per cent. Rib resection for drainage was performed in thirty-six, with a mortality of 44.5 per cent. Rhodes, in 1915, reported eighty-six collected cases of purulent pericarditis with a mortality of 47.7 per cent. That little progress has been made in lowering mortality is indicated by the mortality of 40 per cent in a series of forty-nine cases collected since 1897 (Porter, Eliot, Rhodes). While mortality will always be high because of the serious nature of the disease conditions with which pericarditis with effusion is associated, any lowering of mortality will probably be through earlier diagnosis and treatment, thus forestalling myocardial degeneration, and through more adequate drainage of the postcordial recesses.

Since pericarditis is essentially a complication and not a primary disease, the prognosis and results of surgical treatment must necessarily depend to a great degree on the nature and severity of the primary process. Sears found that of fifty-one patients with pericarditis following rheumatism only 5 per cent died, while of forty patients in whom the condition was associated with other etiologic conditions 80 per cent died. Any attempt to establish the relative merit of various forms of surgical treatment should therefore be through separate studies of results in the various etiologic groups. The available studies furnish the basis for only a very general estimate of mortality and results of treatment.

MAYO CLINIC SERIES

During the last two years nine cases of pericarditis with effusion have been treated surgically at the Mayo Clinic. Four were cases of serous effusion, four purulent, and one hemorrhagic. The primary or associated disease conditions in the cases of serous effusion were: (1) bronchopneumonia following thyroidectomy for exophthalmic goiter; (2) pulmonary tuberculosis, myelogenous leukemia, bilateral pleurisy with effusion, and ascites; (3) bilateral pleurisy with effusion; and (4) bilateral pleurisy with effusion and ascites, Pick's syndrome.

In the first case aspiration of 120 c.c. of serous fluid produced a

remarkable improvement in the whole clinical picture, and the patient progressed to a complete recovery. In the second case 220 c.c. of fluid was aspirated. The patient died the same day. Necropsy revealed bilateral pleural effusion and ascites and acute miliary tuberculosis involving the pericardium, lungs, liver, and tracheobronchial lymph glands. Pericardiocentesis in the third case yielded 50 c.c. of serous fluid. The pleural cavities were aspirated on four occasions, and from 600 to 1,600 c.c. of fluid evacuated. The patient was discharged improved. He died at home six months later. In the fourth case aspiration of 100 c.c. of pericardial fluid was followed by marked improvement. Later the pleural cavities were aspirated, and from 900 to 1,350 c.c. of serous fluid evacuated. *Bacillus tuberculosis* was demonstrated in the sputum. The patient was discharged essentially unimproved and died a few weeks later. Necropsy was not performed.

The suppurative pericarditis in each of the three cases was due to a hemolytic streptococcus, in two, of the epidemic type. In one of these cases the pericarditis developed during convalescence following bilateral dissection of the submaxillary triangles for epithelioma of the lip. At exploratory aspiration 350 c.c. of pus was aspirated through a hypodermic needle. The next day about 200 c.c. of pus was evacuated by open drainage. Dakin's solution irrigation was used in this case, but only after the patient began to show signs of myocardial degeneration following several days of drainage. He died suddenly with symptoms of cardiac failure. Necropsy was not allowed.

The second case was one of epidemic streptococcus bronchopneumonia, with bilateral empyema, following thyroidectomy for adenoma. The empyema was drained by the closed method and Dakin's solution irrigation instituted. Pericardiotomy was performed following two aspirations. The patient died with symptoms of septicemia. The necropsy revealed bilateral empyema with involvement of the myocardium and liver, and with cellulitis of the chest wall.

In the third case primary pericardiotomy was performed with evacuation of 500 c.c. of pus and secondary drainage of both pleural cavities for empyema of 500 and 1,500 c.c. respectively. The pericardial cavity and both pleural cavities were irrigated with Dakin's solution. A biliary fistula developed, which drained into the pericardial cavity. The patient lived several weeks, and seemed to have a fair prospect of recovery, when he developed a sudden left intrapleural hemorrhage, from which he died. Necropsy was not permitted.

Pericardiotomy was performed also on two occasions in a case of chronic tuberculous pericarditis, which clinically seemed primary in the pericardium. At the first operation the pericardium was sutured following evacuation of 2 l. of purulent exudate. A specimen of excised pericardium showed tuberculosis. The fluid reaccumulated. At the second operation the pericardial cavity was left open, but the skin was closed in an attempt to secure subcutaneous drainage. Sufficient time has not elapsed to warrant a statement concerning the ultimate results following this procedure.

In the case of probable malignant hemorrhagic pericarditis aspiration was carried out on fifteen occasions, and a total of nearly 8 l. of hemorrhagic fluid obtained. The site for aspiration was outside the nipple line, fifth interspace, in the costoxiphoid angle, and, after fluid could not be aspirated there, to the right of the sternum. The etiology at the onset in this case seemed very obscure. The Wassermann test was strongly positive and the effusion followed an arsphenamin reaction, but microscopic examination of an excised cervical gland showed adenocarcinoma.

The technic in all these cases has been simple. All operations with the exception of one have been performed at the bedside, under local anesthesia. For aspiration a 20 c.c. record syringe with a 4.5 cm. needle has been used. Pericardiotomy has been performed following resection of the fifth or sixth cartilage, or of both. The pleural cavity has not been opened in any case.

SUMMARY

1. Pericarditis with effusion occurs most frequently in association with acute rheumatism. Other primary disease conditions commonly associated with it are pleurisy, pneumonia, the acute general infections, tuberculosis, and chronic nephritis. In children pericarditis usually follows pulmonary or pleural infection.

2. The most characteristic symptoms are increased precordial dullness, feeble or absent heart sounds, absent apex impulse, small rapid pulse, dyspnea, and cyanosis. The onset may be insidious and the symptoms latent.

3. Exploratory pericardiocentesis may be necessary to establish the diagnosis of the presence of fluid and its nature.

4. Exploratory pericardiocentesis with a short hypodermic needle which infiltrates the tissues with novocain as it enters is as simple and

painless, and will probably prove equally as harmless, as exploratory aspiration of the pleural cavity.

5. The point of election for aspiration seems to be in the region of the left mammary line, fifth interspace, just inside the left border of dullness. In case aspiration here is negative, alternative points are beneath the xiphoid process (Marfan) at the left sternal border and at the right sternal border in the fifth interspace.

6. A negative aspiration at any one point, especially at the left sternal border, does not exclude the presence of fluid.

7. A serous effusion is usually sterile, but it may be infected. A purulent exudate is usually infected, but it may be tuberculous or secondary to malignant disease.

8. Preliminary partial evacuation of any exudate may probably be accomplished during exploration through an aspirating needle and a small syringe.

9. A sterile exudate, except the persistently recurring type, should be evacuated by aspiration through a small short needle.

10. An infected exudate should be evacuated by pericardiotomy after preliminary resection of the cartilage in order to secure wide open dependent drainage.

11. If the patient is critically ill a bedside operation under local anesthesia is especially indicated. Knife section of the cartilage obviates the necessity of freeing it from underneath before it is resected.

12. Owing to anatomic variations in the reflection of the left pleura, a transpleural operation may be unavoidable. In suppurative pericarditis the leaves of the pleura, however, probably are adherent, and thus wall off the pleural cavity.

13. The most dependent parts of the pericardial cavity on each side of the vena cava must be reached in order to secure the most efficient drainage and to prevent possible encapsulation of exudate behind the heart.

14. Irrigation by promoting evacuation of the exudate seems to be a rational measure supplementary to drainage.

15. The mortality rate, which is high on account of the severity of the primary disease conditions, especially those with which purulent pericarditis usually is associated, will probably remain relatively high; however, it may be reduced materially by the earliest possible diagnosis, prompt evacuation of any exudate causing mechanical embarrassment to the heart, and by wide open adequate drainage in the infected type of the disease.

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A CLINICAL STUDY OF FIFTY CASES OF PNEUMOTHORAX*

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In 1803, Itard coined the term pneumothorax to describe the condition of air free within the pleural space. He was able to demonstrate its presence in five necropsies of patients dying of tuberculosis, and he associated the presence of air as a complication of the disease.

It is now the centennial of Laennec's invention of the stethoscope and his discovery of mediate auscultation. To him belongs the credit of first recognizing pneumothorax during life. His description of physical signs, and his classification according to etiology were so complete that little has been added thereto. He also first interpreted the succussion splash to be due to the combined presence of air and fluid in the pleural space. This diagnostic sign was described in the complete works of Hippocrates of the fifth century, B. C., known as "Hippocratic succussion." The authorship is questionable, and it seems certain that Hippocrates and his contemporaries misunderstood the significance of the sign, being misled because of the universal belief that air was normally present in the pleural cavity.

During the early part of the nineteenth century the value of Auenbrugger's discovery of percussion and of Laennec's auscultation had been properly evaluated, and in those years a fineness of description and an accuracy of examination developed that we would do well to imitate. To the great clinicians of that day accurate histories and painstaking examinations were necessarily of primary importance. Few laboratory tests could contest their place in diagnosis, and they had not the roentgen ray to tempt them from clear thinking and accurate work.

Pneumothorax has acquired a new interest since Forlanini, in 1888, and Murphy independently, in 1898, utilized artificial pneumothorax in the treatment of certain types of tuberculosis. The method was coolly received for a few years, but has recently enjoyed a vigorous revival.

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Again during the Great World War it was found that not all of the physiology of pneumothorax was understood.

Many lives were sacrificed before the problem of high mortality following early operation in empyema was solved.

Even today, with regard to the treatment of the condition and its complications, opinions are far from uniform. This is especially true of the cases presenting urgent symptoms.

The fifty cases in this series are discussed for the purpose of calling attention to the need of greater utilization of common methods of physical diagnosis in order to point out certain defects in our knowledge of the condition, to indicate distressing complications of certain methods of treatment, and, finally, to reach rational methods of treatment based on our experience and the consensus of opinion of men who have had opportunities of dealing with this class of case.

THE PHYSIOLOGY OF THE CHEST AS APPLIED TO PNEUMOTHORAX

Physiology fails in many respects to account for the phenomena of pneumothorax, since each case is in a measure a law unto itself. However, certain physiologic principles are basic and should always be kept in mind in interpreting the indications of this condition.

Normal negative intrapleural tension depends on: (1) the fact that at the first respiration after birth "the thoracic cage expands more quickly than the lungs, so that the latter become stretched" by the atmospheric air entering through the respiratory passages, and (2), the fact that the lungs thus stretched tend, by virtue of their elastic tissue, to recoil. Thus when inspiration occurs the lungs are more expanded and negative intrapleural tension is increased, and on expiration the intrapleural tension becomes lessened. The force required to keep an elastic band taut depends directly on the degree of stretching and decreases as it returns to normal dimensions. Thus we have a respiratory fluctuation in intrapleural tension which determines the movement of air in and out of the lungs. As McLeod remarks, "the thorax does not expand on inspiration because air rushes in, but air rushes in because the thorax expands." He gives -5 mm. mercury on expiration and -10 mm. mercury on inspiration as the normal intrapleural tension in man. Aron in thirty-six observations on a normal person found the average intrapleural pressure on expiration to be -3.02 mm. mercury and on inspiration -4.65 mm. mercury.

In studying pressure in necropsies following various diseases we found a negative pressure. If the respiratory passages are blocked and the thorax expands, the intrapleural tension may be as low as -80 mm. mercury.

The mediastinum in the normal subject is a mobile structure held in position by the traction of the elastic tissue of the lungs exerting pull in opposite directions. If open pneumothorax is induced, the lung on that side is collapsed and its tendency to elastic recoil is satisfied. The conditions determining the coaptation of the pleural surfaces on the opposite side remain unchanged and the elastic recoil of the sound lung is partially satisfied by a displacement of the mediastinum toward the sound side. Moreover, respiratory fluctuation of the intrapleural pressure on the sound side occurs with a consequent variation of the tension exerted on the mediastinum and a certain amount of movement of the latter with each respiratory phase. Graham and Bell, from experiments on dogs, found that both lungs become equally collapsed when a unilateral open pneumothorax is produced. They are careful to apply this observation only when the mediastinum is unaffected by disease. Clinical and surgical observations make it doubtful whether this holds in man, due probably to the greater fixity of the diaphragm in the latter. The mediastinum of the dog is a much less rigid structure than in man, and is not imperforate, its rigidity more nearly corresponds to that of the infant. In this connection the remarkable rigidity caused by chronic inflammatory disease should also be remembered. In open pneumothorax the dyspnea depends, other things being equal, on the degree to which the elastic recoil of the two lungs is satisfied. It depends on the open side on the strength and extent of the adhesions that prevent the collapse of the lung. In the absence of adhesions on the open side the degree of the lung's collapse on the sound side depends on the fixity of the mediastinum. In cases occurring suddenly, in which no adhesions exist, the respiratory excursions of the mediastinum and the change in intrathoracic pressure combine to interfere with the normal circulation and add to the gravity of symptoms. Hazard is especially great in cases in which the tidal air approaches the vital capacity, as Graham and Bell have pointed out.

An opening in the chest wall at least as large as a cross-section of the trachea must next be considered. It might be supposed that in this condition the lung would collapse completely and so remain, yet this is not necessarily true, for West observes that it is not an uncom-

mon experience, on opening the chest for drainage of an empyema cavity, to find that the lung which has been completely collapsed by the effusion expands as soon as the pus is evacuated, and nearly approximating the chest walls immediately after operation. This phenomenon has been repeatedly demonstrated in our own experience. When operating for the removal of mediastinal tumor, cough and deep breathing make it difficult to keep the lung within the thorax. West explains the phenomena he describes: "The air in the tubes is not subject simply to atmospheric pressure during the phases of respiration. During inspiration a certain obstruction to the free ingress of air is encountered which produces a subatmospheric pressure in the tubes amounting to 5 mm. mercury. During expiration a similar obstruction to the free egress of air is met, producing a pressure of 1.5 to 2 mm. mercury above that of the atmosphere." He believes that these pressure oscillations are sufficient to expand the lung at least one-half and perhaps more, provided it is unhampered by adhesions. In operative work it is impossible to determine whether or not on opening the chest a lung will collapse. Lockwood believes there is less danger in an opening large enough to admit the hand than in a small one.

In valvular pneumothorax air finds easier access to the cavity during inspiration than issues from the cavity during expiration. During the early stages pneumothorax is always more or less valvular and as soon as the lungs become completely collapsed the lesion becomes completely closed whether it is sealed or not. It is quite possible that some of the grave symptoms believed to be due to valvular pneumothorax are, in reality, due to additional successive rents in the pleura.

By subjecting the bronchial tree to a pressure of 10 cm. of water it is possible to expand the retracted lung in the presence of an external pleural opening. Tuffier states that in applying this procedure the upper lobe expands easily, the middle lobe less so, and the lower lobe least so. From this he concludes that the lower lobe has the greatest elasticity.

Means and Balboni in a study of respiration in persons with pneumothorax found that one lung is as efficient as two, except when the work done calls for more than a threefold increase in normal ventilation. They state that the only difference between normal persons and those with a collapsed lung is that the latter, when called on to increase their ventilation, reach their limit a little sooner than the former.

We are unable to reach definite conclusions with regard to what

occurs in the circulation of a collapsed lung. Cloetta, on the basis of plethysmographic experiments, supports the theory that it is better to irrigate the lung during collapse than during inspiratory expansion. Corper, Simon, and Rensch, working with rabbits, and producing unilateral closed pneumothorax, injected suspensions of Prussian blue, scarlet red, and starch intravenously. These substances were found uniformly distributed through the lungs immediately after injection and two hours thereafter. It was also found that the Prussian blue disappeared uniformly, indicating that the circulation of the two sides was maintained equally. This finding is supported by our clinical observation that lungs that have remained collapsed for a long time may regain complete function without evidence of nutritional disturbance.

ETIOLOGY

The etiologic factors present in the series of fifty cases may be tabulated as follows:

	Cases.
Tuberculosis.....	28
Empyema.....	8
Spontaneous pneumothorax (cause unknown).....	6
Bronchial fistula (nontuberculous).....	3
Traumatism.....	3
Therapeutic measures (artificial).....	3
Emphysema.....	2
Lung abscess.....	1
Thoracentesis (accidental during).....	1 (Fatal with needle)
Pneumonia (complication).....	1
Lymphosarcoma (complication).....	1

It will be observed that the cases tabulated total more than fifty; two factors were present in some of the cases and the real cause of the pneumothorax could not be determined. As an example of this overlapping, pneumothorax was induced as a therapeutic measure in three cases, in two of tuberculosis, and in one of lung abscess. Emphysema was claimed to be the cause of the pneumothorax in two cases in which other factors were ruled out by careful study and in which emphysema was known to be present. Five cases classified as spontaneous fulfilled Hamman's definition except that in two cases the pneumothorax persisted more than eight weeks. In one of these the history made it very probable that there had been successive attacks which prolonged the period of absorption. We believe then an arbitrary time limit as an absolute criterion of diagnosis of spontaneous pneumothorax is

unwarranted, and that the findings peculiar to each case can alone determine to which group it should be attributed.

Nineteen cases of simple pleural effusion in the series were previously aspirated on an average of two and eight-tenths times. It is impossible to know how many times aspiration was responsible for air in the pleural space. It must not be assumed that the pneumothorax following aspirations is necessarily due to leakage through the needle. Puncture of the lung may provide the means for entrance of air from the bronchial system. This was clearly demonstrated in a recent case not included in the series in which an exploratory puncture was made. The needle pierced the lung and at necropsy the rent was found patent and promptly emptied the lung after inflation. The escape of air could be detected coming from the puncture opening when the inflated lung was immersed in water. It was difficult for the artist to obtain a proper view of the lung as it became too promptly deflated. The lung was emphysematous, and the results might not have appeared in a normal lung. We have repeatedly demonstrated the same condition in lungs punctured after death, when normal elasticity seems to have been interfered with.

From a study of the literature we find a general agreement that tuberculosis is the cause of pneumothorax in from 75 to 90 per cent of cases. Thus Biach's oft quoted 918 cases occurring in the Vienna hospitals show that 715 (77 per cent) were due to tuberculosis. West estimates that 90 per cent of cases are due to perforation of the lung because of the breaking down of a tuberculous focus. Pneumothorax has been observed as a complication of tuberculosis by Galliard in 36 of 3,415 cases (1 per cent); by West in 5 per cent of cases, by Fowler and Rickman in 6.5 per cent of 1,000.

As a rule pneumothorax occurs in the cases of tuberculosis in which the disease is advancing rapidly, though it may occur from the rupture of a small tuberculous nodule near the periphery of the lung when no other tuberculous foci are discoverable elsewhere in the lung. Letulle, in two excellent illustrations of pathologic specimens, shows the method of perforation, and emphasizes the fact that pleural adhesions are potent factors in preventing the collapse of the lung. He states that a single perforation is rare, and West points out that in twenty-five perforations two openings occurred in four cases, and four each in two cases; the openings occurring twice as often in the upper as in the lower lobe and usually being not more than from 2 to 3 mm. in diameter.

In nineteen of these twenty-five cases necropsy was performed within a week and the opening was still patent; in six cases the openings remained open for from thirteen days to five months. This shows that the opening often may persist for months.

Pneumothorax furnishes strong presumptive evidence of tuberculosis and, conversely, air in the chest as a complication of known cases of pulmonary tuberculosis must always be looked for.

We are inclined to regard pleural adhesions as a protective process against the accident of perforation. If there are adhesions of sufficient strength, pneumothorax does not exist. It occurs at the advancing edge of the disease, probably because of the insecurity of union between the visceral and parietal pleuras. We believe that if this were not true the complication would appear in a very much larger percentage of cases. The presence of apical pleurisy is a benignant process of conservation.

DISCUSSION OF LITERATURE

An extensive literature has accumulated around the cases classified spontaneous pneumothorax. Hamman has best defined this condition as "A pneumothorax coming on in apparently healthy individuals without ascribable cause; resulting in no infection of the pleura and therefore unaccompanied by constitutional symptoms and healing rapidly and completely in a few weeks." He believes a duration greater than eight weeks makes it doubtful whether the case should be denoted spontaneous. Zahn is quoted as ascribing this type of pneumothorax to one of four mechanisms: (1) The rupture of a vesicular bleb, (2) the rupture of interstitial emphysema blebs which finally make their way to the pleura, rupturing through it, (3) the direct tear of the pleura by the tug of adhesions, and (4) senile atrophy of the pleura. Hamman noted sixteen instances in the literature of recurrences of pneumothorax. In three of these and in one of his own series the recurrences were on the opposite side. Abt and Straus and Meyer report two cases of spontaneous pneumothorax with necropsies which demonstrated emphysema to be the etiologic factor. In the latter case the pneumothorax was recurrent and involved both sides for a period of at least twenty-four days. Hewlett and Leclerc each add a similar case in which the patient recovered, though the second side was not involved until the first side had partially returned to normal. These cases denote the margin of safety inherent in the

lungs, and show that bilateral pneumothorax is not immediately fatal unless it is approximately total in both pleural spaces at the same time.

Emerson regarded aspiration as responsible for the condition in ten of forty-eight cases which he reports, and he postulates no less than seven ways in which this accident could occur, the commonest of which are the probable injury to the lungs by the needle, the creation of a negative pressure which may cause the rupture of a superficial cavity or an emphysematous bleb, or the tearing of the visceral pleura at the site of adhesions. Galliard records a case of pneumothorax due to injury of the lung by the aspiratory needle similar to one of Emerson's cases. West asserts that he has repeatedly observed the lung to burst under aspiration. Such an accident becomes of serious moment when it is recalled that it incurs not only the danger of a sudden pneumothorax but also the risk of infecting the pleural cavity from an infected lung.

SYMPTOMATOLOGY AND DIAGNOSIS

Forty-two of the fifty patients (84 per cent) were males. Twenty-four (18 per cent) were in the third decade; seventeen (34 per cent) were in the fourth decade, and six (12 per cent) were in the second decade, making a total of 96 per cent in these three decades. This age incidence will be recognized as the period in which tuberculosis is most active. The age incidence is as follows:

Patients from twenty-one to thirty years.....	48 per cent
Patients from thirty-one to forty years.....	34 per cent
Patients from eleven to twenty years.....	12 per cent
Patients from forty-one to fifty years.....	4 per cent
Patients from fifty-one to sixty years.....	2 per cent

The right side was involved in twenty-eight patients and the left side in twenty-two.

The onset of pneumothorax may be sudden, insidious, or silent. In seventeen cases only the onset was acute with stormy symptoms of dyspnea, severe pain, cough, or shock, which is so frequently described. In nine cases the onset might be described as insidious in which the symptoms were mild, gradually growing more annoying, but never becoming extremely urgent. In one case it seemed likely that there were successive accessions of air to the pleural cavity with corresponding increase in symptoms. In twenty-four cases the onset may be said to have been silent, for the histories did not record symptoms at any time

that would lead to the suspicion of pneumothorax. It is precisely this group of cases that is overlooked unless the age incidence of the disease and the fact that tuberculosis is the usual etiologic factor be kept in mind and unless a careful and systematic examination be made of the chest. Seventy-five per cent of these silent cases were revealed only by the roentgen ray and by operative findings.

Pepper, in an analysis of 500 cases histories, found that the onset of pneumothorax was insidious in 115 cases (23 per cent). Fredericq has reported two cases which occurred without symptoms. Rist and Ameuille found at necropsy supradiaphragmatic collections of air which had previously escaped detection. This, they assert, is the usual site of pneumothorax in tuberculous subjects. They believe the accident is often terminal and accounts for the antemorten dyspnea. Sabourin has reported cases in tuberculous subjects in which the pneumothorax occurred in the fissures, remaining interlobar because of pleural adhesions at the periphery of the lung. These cases fall into the group in which there are few or no symptoms, and he holds that amphoric breathing along the fissural line is the sign of greatest importance.

In the cases in our series in which the onset was acute there was sudden pain in the chest, dyspnea and cough either alone or in combination. In a few cases the pain was referred below the diaphragm. In one case the patient had for months been able to produce a splash by shaking the body.

In 10 per cent of the cases there was a history of the patient suddenly raising a large quantity of sputum, a fact that should always arouse the suspicion that pneumothorax may have occurred.

In interpreting physical signs it must be borne in mind that one is likely to find fluid complicating pneumothorax. In thirty of our cases (60 per cent) fluid was present. No phase of exploration of the chest should be neglected. Inspection may reveal cyanosis, dyspnea, absence of respiratory movement on the affected side, displacement of the heart, and occasionally a filling out of the interspaces on that side. Cruice observed bulging of the chest in 77 per cent of cases, but in our series this was a very infrequent finding except in the cases complicated by a large amount of fluid. Percussion may not yield significant information, as the note may vary, through resonance, to tympany and to dullness. The note may be indistinguishable from that obtained in emphysema or effusion. Thacher attributes the dull note of percussion to air under tension which robs the wall of the chest of its elas-

ticity and thus impairs its resonance. * In our experience the most accurate percussion sign is obtained by the determination of lung motility. In pneumothorax it is found that resonance covers the entire pleural area and is unaffected by inspiratory movement. In the normal lung a shifting of resonance during expiration and inspiration is easily discovered. If maximum inspiratory resonance is maintained during both phases of respiration there is air in the pleural cavity. If, however, pneumothorax is complicated by the presence of fluid, an easily diagnosed shifting dullness and succussion splash provide sufficient data for a positive diagnosis.

On auscultation the coin test was the most constant finding in our cases, and Cruice states that it was present in 90 per cent of his cases. Distant or absent breath sounds are highly important findings. Metallic tinkle was found in only a few cases of the series, and amphoric breathing was an infrequent finding. The absent or diminished excursion of the affected side, distant or absent breath sounds, the bruit d'airain, and the succussion splash are the signs of chief diagnostic importance.

The method of the production of the metallic tinkle is still a subject of controversy. Barach, from an experimental study, concluded that metallic tinkle is produced most typically by a bubble of air escaping from the fistulous opening of a diseased lung below or at the level of the fluid. He asserts that it may be produced by the bursting of a bubble within a bronchial tube when the bronchial tube is connected directly with the air chamber by a fistulous opening of sufficient size, or by a bubble rising from the moist surface of a perforated lung above the level of the liquid when the bubble is expelled with sufficient force. All of these methods presuppose a patent perforation of the lung.

West believes that metallic tinkle may be present in the absence of fluid and is then due to the escape of bubbles of air from the ruptured pleura into the distended pleural cavity. Thacher believes that râles in the neighborhood of large cavities and particularly in pneumothorax set up vibrations whose higher overtones are so pronounced that the sounds become musical tinklings. Rosenbach holds a similar view. Galliard records a case of left-sided pneumothorax in which a metallic tinkle could be heard synchronous with the heart beat when the patient lay on his back, on his left side, or was in a sitting position. Galliard ascribed this to mediate percussion by the heart on the resonant space formed by the distended pleura. We have seen this illustrated in a case of advanced tuberculosis with destruction of the entire left

lung and its area occupied by a large cavity. A pericardiac friction rub could be heard at a distance from the patient as a very high pitched metallic sound. It was accentuated if the patient's mouth was slightly open. We believe this to be due to the amplifying influence of the large air chamber.

A similar difference of opinion exists concerning the genesis of amphoric breathing, some authorities (Thacher, Norris, and Landis) claiming that a patent opening between the lungs and pneumothorax cavity is a necessity. Others believe it may be generated by vibrations propagated from neighboring parts of the lung or bronchial tree (Lord, Fussell, and Riesman). We are of the opinion that both mechanisms can produce it provided the proper tension is attained in the wall of the chest to produce unrhythmic vibrations.

Certain rare symptoms and signs of pneumothorax are worthy of mention. Lublinski records a case in which there was paralysis of the left recurrent laryngeal nerve caused, he believes, by the marked displacement of the heart to the right. The paralysis disappeared when the lung reexpanded and the heart had returned to its normal position.

Honeij reports a case of left pneumothorax with adhesions which prevented complete collapse of the lung in which there were nonexpansile pulsations in the left posterior axillary line from the scapula to the base caused by heart pulsations transmitted through the fluid. Ingram records a case of generalized subcutaneous emphysema, a complication of tuberculous pneumothorax, which appeared first at the root of the neck. Since there was no rent in the parietal pleura he believed that the rupture occurred in the mediastinum, the air from thence making its way along the trachea to the root of the neck.

Williamson, in a study of thirteen cases of pneumothorax and hydro-pneumothorax, found that the blood pressure on the affected side was 16.5 mm. mercury lower in the leg than in the arm. He attributes this to intrapleural pressure on the descending aorta.

An interesting, and probably not infrequent, occurrence is the onset of pneumothorax with abdominal symptoms. Beardsley reports such a case in a patient with tuberculosis of the lungs and bowels in which the onset was sudden with acute pain to the left of the umbilicus, and muscular rigidity which led to the suspicion that an ulcer had perforated. At necropsy two days later there was no perforation, but a left pneumothorax with marked displacement of the heart was found; this condition had not been considered before death.

During the influenza epidemic in 1920, we observed two cases in which empyema began with pain and board-like muscular rigidity simulating acute abdominal crises. We believe this to be referred pain through the seventh to the twelfth dorsal segments. Pneumothorax was not a complication and both patients recovered. The effect of fluid and air on pleura, however, is identical.

Sampson, Heise, and Brown have made a study of pulmonary and pleural annular shadows observed in roentgen examination of fifty patients. These shadows were formerly interpreted as intrapulmonary cavities, but further studies led the authors to conclude that the shadows occur in patients who are probably suffering from pulmonary softening, and they indicate a rupture of the lung. These localized pneumothoraces usually occur in the upper part of the great oblique fissure and in the horizontal fissure on the right; they may have a mural location. They frequently contain fluid and thus present fluid level which may be seen to shift when the patient changes position during fluoroscopic examination. The annular shadows surround areas of increased or equal absorption of the ray. These authors assert that such pneumothoraces can rarely be diagnosed clinically. They were found in 11.8 per cent of 423 cases.

If the physician rarely primarily discovers these shadow-like rings, he often excludes a true cavity by clinical diagnostic methods. In one of the cases of our series a shadow of this type was discovered and diagnosis of pulmonary cavity was made by the aid of the roentgen ray. Examination of the chest in the region of the ring revealed that whispered pectoriloquy, cavernous or amphoric breathing, gurgling or consonating râles were absent. Over this area percussion yielded a tympanitic note and pleuritic friction sounds were heard which, taken with the fact that the ring occurred over the right lower lobe, made the diagnosis of intrapulmonary cavity untenable.

Fishberg, in an earlier article, called attention to these localized pneumothoraces. In differentiating them from pulmonary abscess he points out that in the latter moist consonating râles, bronchophony, and an absence of metallic tinkle or amphoric breathing may be noted. In the former, he emphasizes the sudden onset, the absence of adventitious sounds, the presence of metallic tinkle, amphoric breathing, and whispered pectoriloquy; these signs are most suggestive when heard high in the axilla.

False pneumothoraces, which may be defined as extrathoracic col-

lections of air, must be excluded. Lebon, in a roentgenologic study of these cases, found that the stomach, distended with gas, projected far into the left side. In one case the heart was displaced to the right, and in one an air bubble in the stomach lay between the left margin of the heart and the wall of the chest. Stivelman asserts that hydropneumothorax may be simulated by cases in which the diaphragm is in a high position due either to extreme pulmonary fibrosis or gastrectases, and that these extrapleural pouches are characterized by their failure to absorb the contained gas, the fluid level varying with food ingestion and the emptying of the stomach. On fluoroscopic examination a barium bolus may be seen to enter the supposed hydropneumothorax. Thus the roentgen ray is an indispensable adjunct in the diagnosis of pneumothorax, especially in the localized and the so-called false varieties.

PROGNOSIS

The prognosis of pneumothorax is largely the prognosis of the pulmonary lesion which it complicates. If it occurs in tuberculous subjects, the outcome will depend largely on the degree of involvement of the lung by the tuberculous process. In a few cases pneumothorax results from the rupture of a solitary nodule of the lung with no discoverable pulmonary lesions elsewhere, as in the cases cited by Weber. These cases obviously offer a more hopeful prognosis than those in which extensive and rapidly advancing disease of the lung is a complication. Pneumothorax occurs chiefly in the rapidly advancing type of pulmonary tuberculosis or in the terminal stages of the disease, and hence is regarded as a grave prognostic sign.

In the analysis of fifty-one cases of pneumothorax in tuberculous subjects Morse states that the pneumothorax is the cause of death in 60 per cent; that 80 per cent of the patients die in less than one year, and that 10 per cent live more than five years. West, in an analysis of 101 cases of tuberculous pneumothorax, states that the mortality was 65.4 per cent. In thirty-nine of these patients the duration of life was known: 75 per cent died within the first fortnight and 90 per cent within a month. The presence of annular shadows indicated a somewhat graver prognosis in the series of cases studied by Sampson, Heise, and Brown. In all cases the prognosis further depends on the rationality of the treatment adopted both with respect to the general supportive measures and to the operative treatment employed in com-

bating urgent dyspnea, and in the management of collections of fluid or pus in the chest.

Fussell and Riesman collected from the literature in 1902 fifty-six cases in which there was but a single death from spontaneous pneumothorax. In five of our cases classified as spontaneous there were no deaths. However, in a later case not included in the series the patient was seized with symptoms of urgent dyspnea following an operation for extirpation of the lacrymal sac, and death followed in five hours under expectant treatment. A previous careful examination had not revealed evidence of pulmonary disease and the case was classified as spontaneous pneumothorax. As a whole, the patients with spontaneous pneumothorax have the best outlook, provided they weather the storm of the sudden onset.

Six deaths are known to have occurred in our series of fifty patients, one from influenza, one from abscess of the lung, and four from the combined effects of advanced tuberculosis and empyema. It has not been possible to obtain data concerning the remaining patients long enough to make our mortality statistics of value.

TREATMENT

The part which Emerson believes aspirations play in his cases has been pointed out herein. Previous to entering the Clinic nineteen of our patients were aspirated on an average of 2.8 times. No doubt pneumothorax and what is perhaps its most serious complication, infection of the pleural cavity, might be avoided in many instances if aspirations were practised less frequently or if they were performed by men more experienced in surgical technic. Only the most careful technic is permissible in these cases. We believe that expectant treatment is insufficient in the urgent cases. Paracentesis should be tried; this view is supported by Fussell and Riesman, Meyer, Lord, Rosenbach, Finlay, and Weber. Lord, and especially Rosenbach, prefer to give conservative methods a thorough trial first. West considers aspiration dangerous, and uses a fine trocar or needle to which he attaches a rubber tube, the latter being allowed to open under sterile water. This method commends itself as the one calculated to do the least injury. In referring to the danger of reopening the perforation, Finlay aptly remarked that "it is better to run the risk than to allow the patient to die from asphyxia." Marshak and Craighead report six cases of sudden pneumothorax occurring during the course of induced pneumothorax.

Their patients were successfully treated by repeated aspirations controlled by manometric readings. Sufficient air was withdrawn to relieve the dyspnea, but not enough to allow the lung to reëxpand. The method is certainly logical, but requires a special apparatus and some skill in its use. Finally, a great many patients under expectant treatment promptly adjust themselves to the new circulatory and respiratory conditions. However, it is probably better to perform a paracentesis a little too early than to delay too long.

We consider that aspiration in hydropneumothorax is indicated only for diagnostic purposes or to relieve urgent dyspnea. The most serious danger of repeated aspiration, aside from that creating a superadded sudden pneumothorax, is the danger of converting a hydropneumothorax into a pyopneumothorax, a sequence that had occurred in five of our tuberculous patients before we saw them. Rosenbach, in speaking of paracentesis, in such cases says, "If the exudate is at all large two or three repetitions of the procedure, even when carried out with the greatest care, are practically certain to produce putrefaction and lead to rapid loss of strength."

The treatment of pyopneumothorax follows the principles of the treatment of ordinary pyothorax except the taking into account of the underlying lesion of the former, which is frequently tuberculosis complicated by a pyogenic infection, a condition peculiarly refractive to ordinary methods of treatment and one warranting a very guarded prognosis.

All writers agree that pneumothorax as a therapeutic measure in tuberculosis is indicated in repeated hemoptysis. Robinson and Floyd advocate its use in cases advancing in spite of the usual methods of treatment. Morris, among other indications, advised the use of the method in recent progressive ulcerative lesions with slight activity in the opposite lung. The measure was employed for two of our patients; one was given twenty injections over a period of seven months. A hydropneumothorax and a greatly thickened pleura resulted. Another patient having had a number of air injections developed a series of sinuses at the site of injections and a pyopneumothorax. These results do not necessarily condemn the method, but point out possible dangerous sequelæ. We agree with Kendall and Alexander that pleural effusions, especially if they are purulent, are serious complications. They are believed to occur as a complication of artificial pneumothorax in from 20 per cent (Kendall and Alexander) to 50 per cent of cases.

Simon and Swezey have reported a case of lung abscess successfully treated by two injections of air into the pleural space. One of our patients had been treated in this manner for four months and presented himself with a pneumothorax and an abscess of the lung. His chest was aspirated five times, rib resection was performed twice; the patient finally died from pulmonary hemorrhages. It is questionable whether one should temporize with such a method, for it seems inadequate in dealing with such a serious disease. Although the procedure will not induce the cure for pulmonary diseases that may have been expected, yet we believe, with carefully selected cases and careful examinations, artificial pneumothorax has won its place as a worthy therapeutic procedure.

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OPEN PNEUMOTHORAX IN ITS RELATION TO THE EXTIRPATION OF TUMORS OF THE BONY CHEST WALL*

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Perhaps no surgical condition of the chest is more germane to the discussion of pneumothorax than that of tumors of the bony chest wall. Such tumors are usually either malignant or potentially malignant, and often involve an extensive portion of the wall of the thorax. Complete extirpation with a wide margin necessitates an extensive resection, and furthermore, this operation, usually performed in one stage, results in a sudden collapse of the lung. In contrast to conditions following surgery for infectious diseases, there are no inflammatory adhesions of the pleuræ, and no thickening and fixation of the mediastinum. The posture of the patient, which is usually lateral or dorsal, is favorable to the collapse of the lung and to the transmission of atmospheric pressure to the other side. The operation is concerned with the chest wall and not with the lung; retraction of a lobe of the lung outside the wound is neither necessary nor convenient during resection. There is consequently no steadying of the mediastinum brought about in this way. A study of operative pneumothorax incident to the resection of tumors under such conditions should be of importance both with respect to the theoretic and the practical considerations of the subject.

Resection of the entire chest wall with wide opening of the pleural cavity was practised before the nature of pneumothorax or the dangers incident to it were adequately conceived. The first case of thoracotomy for tumor was recorded by Osias Aimar, who, in 1778, removed an osteosarcoma involving the fifth, sixth, and seventh ribs, but he did not open the pleura. The first case of thoracotomy for tumor in which pneumothorax resulted was reported, in 1818, by Richerand, who, with the assistance of Dupuytren, widely opened the pleural cavity by resecting a portion of the pleura with a carcinomatous growth involving the ribs. Richerand describes the onset of the pneumothorax as follows:

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"At this moment the exterior air made an eruption into the chest, rushing in with violence and compressing the left lung which, with the heart, was borne toward the orifice. I sought, by placing thereto the left hand, to moderate the entrance of air and to prevent suffocation, which appeared imminent, while with the right hand I applied to the wound a large bolster spread with cerate. The entrance of air was suddenly stopped by this greasy cloth." The patient recovered from the operation, but died of recurrence one month later.

It was not until 1855 that Sedillot performed the second recorded intrapleural operation. In an exhaustive review of the literature from then until 1898 Parham was able to collect twenty-six cases in which resections were performed without opening the pleural cavity, and fifty-four, including two of his own, in which it was opened. In twenty-three additional cases of resection of the sternum, pneumothorax resulted in six. In one instance both pleural cavities were opened, with resulting bilateral pneumothorax. The patient recovered. In considering the effect of pneumothorax Parham classified forty-one selected cases into three groups: (1) those in which little or no disturbance followed opening of the pleural cavity, sixteen cases, (2) those in which there was moderate disturbance, ten cases, and (3) those in which there was marked disturbance, ten cases. He concludes that the size of the opening and the duration of the open pneumothorax are the most important factors in producing symptoms. He found that the respiration was interfered with to some extent in all, and that seven of the patients suffered severe collapse. In cases of extensive resection involving adjacent structures, such as the diaphragm and pericardium, he accredited the serious symptoms to the prolongation of the operation rather than to the severity of the procedure.

In 1898, Parham used the differential pressure method of Fell-O'Dwyer in operating on a patient with chondrosarcoma. He employed the positive pressure to inflate the lung, which was then sutured to the parietal pleura, after which he dispensed with the apparatus. A thorough search of the literature has brought to light reports of sixty-seven cases of chest wall tumor in which operation was performed since Parham's first patient was operated on under differential pressure. This includes twenty-eight cases reported by Lund, in 1913, and one case in which he operated under intratracheal insufflation. The case reports of Gross, Stukkei, Hervy, Degorce, Palleroni, and Zschucke unfortunately were not available for this study.

The records of the Mayo Clinic since 1910 contain the histories of forty-nine patients with tumors of the bony chest wall. A complete report of these cases has been published recently.⁶ Fifteen have been included in this study as having a bearing on the theme; with the fifty-eight cases from the literature the total is eighty-two cases.

OPERATIONS UNDER DIFFERENTIAL PRESSURE

Eighteen (about 20 per cent) of the eighty-two patients were operated on under differential pressure anesthesia. The type of differential pressure apparatus used was the Fell-O'Dwyer apparatus in one operation; Brauer's positive pressure chamber in four operations; Sauerbruch's negative pressure chamber in six; and Murphy's chamber in one operation. Intratracheal insufflation was used in four operations and intrapharyngeal insufflation in two.

Chloroform anesthesia was used in five operations, ether in eight, nitrous oxid and oxygen in one, and the anesthetic was not mentioned in four.

The resection was performed for chondroma in three, for sarcoma in nine, for endothelioma in one, for recurrent carcinoma following amputation of the breast in four, and for chronic inflammation in one.

The opening in the chest wall was stated or was inferred by the context to be small in one case (4 cm. in diameter); moderately large ("handteller Grösse") in eight, and large (10 by 18 cm.) in six. In one case the size of the opening could not be determined and in two an opening was not made in the pleura.

The symptoms referable to the opening of the pleural cavity were weak, rapid pulse, and disturbed respiration in the two cases of Porter and Payr. In both of these cases the diaphragms were resected, and the symptoms promptly abated. Pleural effusion occurred in one patient as a postoperative complication. Porter's patient died on the fourteenth day, and purulent bronchitis and pneumonia were found at necropsy.

OPERATIONS WITHOUT DIFFERENTIAL PRESSURE

Sixty-four patients were operated on without differential pressure. The ribs and adjacent structures included in the resection are listed in Table 1.

TABLE 1
EXTENT OF RESECTION

	Cases.	Structures resected with ribs.							
		Clavicle and sternum.	Diaphragm.	Cartilages.	Diaphragm and peritoneum.	Diaphragm, pericardium, and lung.	Sternum.	Lung.	Pericardium.
One rib.	11	2	1	..	..	..	..	..	1
Two ribs.	20	4	2	..	1				
Three ribs.	18	..	3	..	1	..	1		
Four ribs.	15	..	3	..	..	1	..	1	
Five ribs.	1								
Sternum.	11	5	..	2					
Vertebra.	1								
Structure not mentioned.	7								
Total.	84	11	9	2	2	1	1	1	1

Chloroform was used for fifteen patients, gas and ether for one patient, and ether for fourteen patients; the anesthetic for the others was not mentioned. Pneumothorax was produced in forty-three of the patients, in two bilaterally. In the remaining twenty-one patients the pleura was not opened, or there were extensive adhesions.

In the forty-three cases in which the pleural cavity was opened without differential pressure with resulting pneumothorax the opening was stated or inferred to be small in nine, moderately large in three (about 7 cm. in diameter), and large in twenty-three. In the other cases the size of the opening was not mentioned. In several the opening was so large that "both hands could be introduced at once into the pleural cavity."

It may be noted in Table 2 that of the forty-three patients in whom pneumothorax was produced there were symptoms referable to it in nine, and there were no symptoms in twenty-six. Symptoms were not mentioned in eight. Postoperative symptoms were designated as shock in nine; there were no symptoms in eighteen, and no mention of symptoms was made in sixteen. Of the patients without pneumothorax there was postoperative shock in three, no symptoms in ten, and no

TABLE 2

SYMPTOMS AT THE TIME OF OPERATION AND AFTER OPERATION

Patients operated on with differential pressure anesthesia without pneumothorax.		Patients operated on without differential pressure anesthesia.	
		With pneumo- thorax.	Without pneumo- thorax.
Shock at the time of operation	3	5	
Shock after operation	1	9	3
Cyanosis at the time of operation	..	3	
Cardiac collapse at the time of operation	..	1	
No symptoms at the time of operation	6	26	10
No symptoms after operation	7	18	10
Symptoms at the time of operation not mentioned	9	8	11
Symptoms after operation not mentioned	10	16	8
Total number patients having symptoms at the time of operation	18	43	21
Total number patients having symptoms after operation	18	43	21

mention of symptoms in eight. Table 2 shows, therefore, that while the majority of the patients with pneumothorax do not have marked symptoms referable to it, and only a very small percentage have symptoms at the time of operation, the incidence of postoperative shock is considerably greater if pneumothorax is produced. That this is largely due to the relatively greater extent of the operation on the latter is apparent from the fact that of the nine patients with marked shock after operation six had resections of adjacent structures, namely, the pericardium, the diaphragm, and in one case the lung.

Table 3 shows that in five cases in which the opening into the pleural cavity was small, no symptoms were present in 80 per cent; in twenty in which the opening was large, no symptoms were present in 70 per cent; and marked symptoms were present in only 20 per cent. In the seven cases in which the opening was very large there were no symptoms in two, slight symptoms in two, and marked symptoms in three. In the three with marked symptoms the diaphragm was also resected in two; after suture the symptoms subsided.

TABLE 3
RELATION OF SYMPTOMS TO SIZE OF PLEURAL OPENING

Size of opening.	No symptoms.	Slight symptoms.	Marked symptoms.	Symptoms not mentioned.	Total.
Small.....	4	1	..	4	9
Moderate.....	1	2	..	..	3
Large.....	14	2	4	3	23
Total.....	19	5	4	7	35

Sufficient data were not forthcoming on which to base any observation as to the relation between the length of time the pleural cavity was opened and the relative incidence of symptoms. The depth of anesthesia, the relative conditions of the patients, and the position on the operating table are additional factors which produce uncertainty in attempts to estimate the direct relationship of the pneumothorax and the symptoms. In the absence of symptoms, however, it may be assumed that the pneumothorax was relatively harmless.

In several cases in the Mayo Clinic series it was well shown that the extent of the operation plays a large part in the production of shock entirely independent of pneumothorax. Several of the patients were practically pulseless after leaving the operating room following resection for large tumors without opening of the pleural cavity. Loss of blood was slight and in no case was the operation very long. Some of these patients were in fairly good condition; others were poor surgical risks. A two-stage or three-stage operation was performed in the latter cases. That a resection of the structures of the thoracic wall in itself produces shock is demonstrated in certain cases of radical amputation of the breast. Considerable shock may result in a patient who was a relatively good operative risk.

From Table 4 it will be observed that 11 per cent of patients operated on under differential pressure anesthesia developed complications, while 28 per cent of patients operated on without differential pressure anesthesia in which pneumothorax occurred, developed complications. Pleural effusion, both serous and purulent, is of much greater incidence in cases in which pneumothorax is produced.

Table 5 shows that one death occurred on the fourteenth day in the patients operated on under differential pressure anesthesia; this

TABLE 4
POSTOPERATIVE COMPLICATIONS IN RELATION TO PNEUMOTHORAX

	Patients operated on with differential pressure anesthesia.	Patients operated on without differential pressure anesthesia.	
		With pneumothorax.	Without pneumothorax.
Bronchitis.....	..	..	1
Pneumonia.....	1	2	
Pleurisy with effusion.....	1	4	
Empyema.....	..	5	
Pulmonary congestion.....	..	1	
Anuria.....	..	..	1
Total.....	2	12	2

TABLE 5
POSTOPERATIVE MORTALITY

Cause of death.	Patients operated on under differential pressure anesthesia.	Patients operated on without differential pressure anesthesia.	
		With pneumothorax.	Without pneumothorax.
Pneumonia.....	1	1	
Empyema.....	..	3*	
Shock.....	..	2	
Anuria.....	..	..	1
Not given.....	..	1*	
Total.....	1	7	1

* Double pneumothorax in one case.

case was reported by Porter, who considered the differential pressure anesthesia largely contributory to the unfavorable outcome. One of the patients in the Clinic died of pulmonary edema the second day following operation for intrathoracic tumor under intratracheal anesthesia. Seven deaths followed operation in the cases in which differential pressure was not used and in which pneumothorax occurred; in two of these, however, a bilateral pneumothorax had been produced.

The mortality rate was about 5.5 per cent for the first group and 16.3 per cent for the second. If the cases of shock, which may have been due to other causes, are subtracted, the mortality rate drops to about 11 per cent. Pneumothorax did not occur in the patient with anuria.

DISCUSSION

The cases presented and the results obtained have significance in relation to the question of the actual immediate risk of open operative pneumothorax and in relation to postoperative complications. It is obviously not only possible, but reasonably safe, so far as the immediate risk to the life of the patient is concerned, to open wide the pleural cavity without differential pressure anesthesia. The experience of many operators has shown that in the majority of patients in whom a large opening of the pleura has been produced, with collapse of the lung, symptoms have been absent or slight. Furthermore, it is always possible to convert a large opening into a small opening, or completely to close the opening by drawing together the skin edges or by covering the opening with a wet towel. Experience has also seemed to show that traction on the lung will promptly relieve alarming symptoms referable to inefficient respiration. Whether the apparently slight effect produced by wide open pneumothorax in so large a proportion of cases is due to a previous thickening of the mediastinum or to partial adhesions of the lung may be questioned. It is certain that there was massive collapse of the lung in many cases, but even granting the presence of a thickened mediastinum and possibly adhesions, and if it is further admitted that patients without thickened mediastinums and without adhesions would become asphyxiated by a large opening, the objection to operating without differential pressure anesthesia in such cases would be largely overcome by the fact that when alarming symptoms are presented it is a simple matter to convert the open pneumothorax into a closed pneumothorax.

From a technical standpoint, however, an operation under differential pressure anesthesia can unquestionably be performed with greater assurance, less disturbance to the patient, and greater comfort to the surgeon. The impracticability to the average operator of differential pressure anesthesia chambers and the technical difficulties incident to the use of intratracheal insufflation and of other apparatus must be taken into consideration.

A study of these cases in relation to postoperative complications,

with their increased mortality, indicates that the increased occurrence of complications furnishes the greatest support for the use of differential pressure anesthesia in resections for tumors of the chest wall. It has been demonstrated clinically and experimentally by Noetzel, Tiegel, Burkhardt, and others that pneumothorax renders a pleural cavity less resistant to infection. Robinson and Sauerbruch showed that a sterile pleural effusion may develop, apparently due to the lack of contact between the pleuræ. The presence of a dead space would also seem to further a postoperative infection. The tendency to localization, as in the peritoneal cavity and to some extent in the normal pleural cavity, is absent. The aspiration of the air into the pleural cavity at operation probably also increases the risk of pulmonary infection. This could be largely obviated, however, by the use of gauze protection, as in abdominal surgery.

Empyema was the most potent cause of death in this group of cases; and it is reasonable to believe that the presence of pneumothorax at least contributed to the development of this complication. Therefore, from the standpoint both of maximum safety to the patient and of technical facility, differential pressure anesthesia is preferable in any case in which the thorax is likely to be opened wide and to remain open for some time. The greatest argument in favor of differential pressure anesthesia seems to rest in the fact that the development of postoperative complications, particularly pleural effusion, is apparently lessened by its use. This advantage may be gained, however, possibly equally well by some method of insuring inflation of the lung at the end of the operation. In view of the advantages of local anesthesia for a preliminary incision, rib resection, and so forth, a combination of local anesthesia with some type of differential pressure anesthesia apparatus would make possible the inflation of the lung at the end of the operation before closure. This method was used in one case in the series in the Clinic and represents a maximum of simplicity and of operative and postoperative safety to the patient. A simple intrapharyngeal insufflation anesthesia by the use of a gas and oxygen apparatus achieves this result.

The foregoing deductions seem justified by the actual experience of many surgeons with different methods and by my experience with ten patients, some of whom were operated on with differential pressure anesthesia, and others without it. Although I have not entered into a discussion of the pathologic physiology of pneumothorax, I wish to

point out that the explanation of the phenomena incident to pneumothorax is not simple.

The work of Graham and Bell, showing that in the normal thorax the pleural cavities function as one and that a change in pressure in one cavity is immediately transmitted to the other, seems fundamental to the study of the problem. This principle accounts for the prompt relief that results on converting an open pneumothorax into a closed pneumothorax, and for the relief obtained by traction on the exposed lung. It remains to be shown, however, why such a large proportion of patients do not develop alarming symptoms when the thorax is opened wide.

The symptoms produced in open pneumothorax are referable in the last analysis to disturbed circulation, to deficient aëration of the blood, and, possibly in some cases, to a pleural reflex. The return of the blood to the right side of the heart is dependent on the force of the heart's action through the capillaries, on the valve action in the veins, on the muscle tone as pointed out by Mann, and on the aspirating effect of the respiratory pump. In open pneumothorax this aspiratory action is lost, and cynosis and engorgement of peripheral veins develop. Deep anesthesia, resulting in loss of peripheral tone, further hampers venous return. Deficient venous return results in a lowered output from the heart, increased pulse rate, and eventually in a fall of blood pressure and shock. A positive pressure anesthesia apparatus provides for aëration of the blood, but does not furnish a substitute for the aspiratory action of normal respiration. Sauerbruch holds that, on the contrary, positive pressure impedes the circulation in the lungs.

Considerations which bear on the aëration of the blood are the relative amounts of blood passing through a collapsed lung as compared with that passing through a normal lung, the relative importance of the paradoxical respiration in the collapsed lung, the part played by the diaphragm, and the possible influence of disturbed nerve function. Other problems relate to the increased susceptibility of the pleural cavity in pneumothorax, to effusion and infection, and to the possible part of a pleural reflex in the sudden onset of symptoms incident to the abrupt collapse of the lung.

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SUBDIAPHRAGMATIC ABSCESS*

AMBROSE L. LOCKWOOD

Subdiaphragmatic or subphrenic abscess may be defined as a collection of pus beneath the diaphragm, but in direct contact with it.

Barlow, in 1845, described the condition, Hilton Fagge, in 1873 and 1874, published some interesting observations on it, but it was not until 1879 that the first operation was recorded by von Volkmann.

It is necessary to have a clear mental picture of the anatomic boundaries of the subphrenic space in order to appreciate the possible etiologic factors and the sequelæ of an abscess located in this region. An exact knowledge of the anatomy of the space is also important in determining the nature of the operation necessary to insure the easiest access to the abscess and its complete drainage. The textbook descriptions of the anatomic boundaries and of the extent and route of extension of subphrenic abscesses are vague and indefinite. Barnard's detailed description of the space is probably the most complete for practical purposes; however, it is somewhat illogical and not altogether anatomically correct. He describes six areas on the under surface of the diaphragm: four intraperitoneal and two extraperitoneal. The four intraperitoneal spaces are separated and defined by the crusiform arrangement of the peritoneal folds or ligaments of the liver, namely, the falciform, the coronary, and the right and left lateral ligaments. The right extraperitoneal subphrenic space occupies the uncovered area between the layers of the coronary ligament as they are reflected on to the diaphragm, while the left extraperitoneal space is described as the area above the pole of the left kidney where the peritoneum reflects on to the diaphragm.

The peritoneal cavity may be divided into supracolic and infracolic portions, the former being the portion above the transverse colon, and the latter the portion below. The supracolic area is divided by the falciform ligament into a right and left portion, and these are again divided transversely by the coronary ligament and the right and left lateral ligaments to form four areas: (1) the right anterior intraperi-

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toneal, (2) the right posterior intraperitoneal, (3) the left anterior intraperitoneal, and (4) the left posterior intraperitoneal (Fig. 261).

In the right anterior intraperitoneal space, described by Barnard, the convexity of the liver is below and the corresponding concavity of the diaphragm is above. The falciform ligament forms its medial boundary and behind passes to the right lateral ligament of the liver.

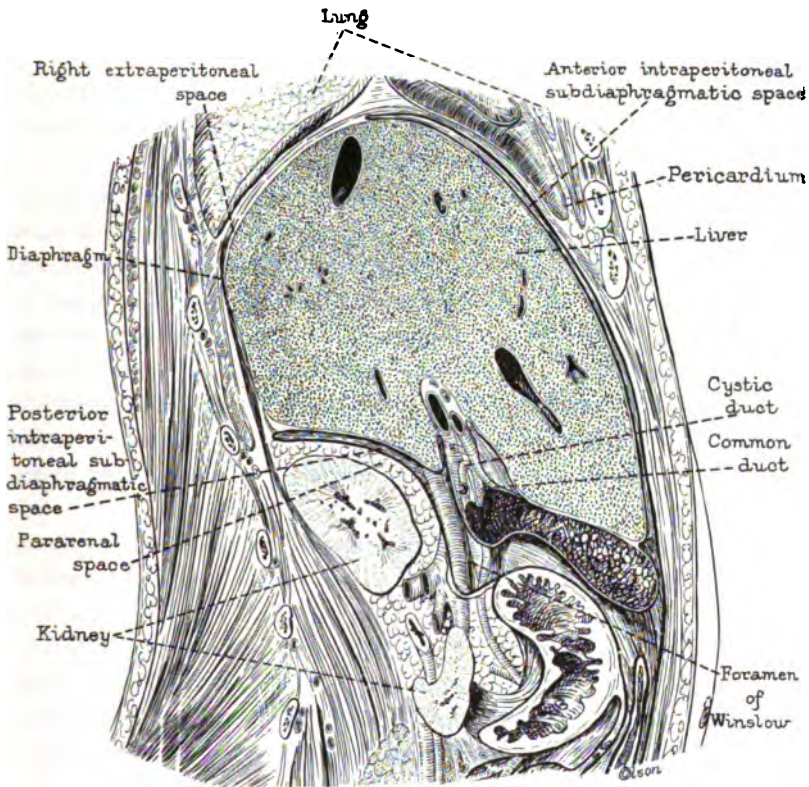


FIG. 261.—Diagrammatic longitudinal section showing the relations about the diaphragm on the right.

If an abscess forms in this space, it is shut off from the peritoneal cavity in front by a variable line of adhesions; usually of the transverse colon and omentum if the etiology is perforating gastric ulcer or duodenal ulcer, but if the etiology is an inflammatory extension from behind or from within the liver, the anterior border of the liver becomes adherent to the diaphragm and itself forms the lower boundary. The right

anterior intraperitoneal cavity has important connections. At its posterior and outer part it communicates around the margin of the liver and around the extremity of the right lateral ligament with the right posterior intraperitoneal cavity or the subhepatic pouch (Morison). At the same point it is directly continuous with the right lumbar fossa or right paracolic groove which lies between the ascending colon and loin, and extends down to the cecum and thence into the pelvis. Because of its location and free connection with adjacent fossæ an abscess develops more frequently in this space than in any of the other subphrenic areas. This space is, in reality, the only true subphrenic space on the right side, and it is questionable if it should not be classified as the right subphrenic space.

The right posterior intraperitoneal space is an irregular pyramidal-shaped area extending transversely beneath the overhanging margin of the liver. It is bounded laterally by the wall of the abdomen, anteriorly by the liver and gallbladder, and posteriorly by the upper pole of the kidney and crus of the diaphragm; medially the apex is formed by the sloping margin of the left lobe of the liver and by the common bile duct and duodenum. Here it connects through the foramen of Winslow with the left posterior intraperitoneal space (the lesser peritoneal cavity). Above to the right is the right lateral ligament and the liver, and medially (left) the transverse fissure.

If an abscess forms in this area it is walled off below by adhesions between the margin of the liver and the surface of the stomach medially, and below and laterally by adhesions of the great omentum and transverse colon to the margin of the liver and the anterior and lateral abdominal wall. This space is continuous laterally with the right lumbar pouch or paracolic groove and with the right anterior subphrenic space. It connects through the foramen of Winslow with the left posterior intraperitoneal space, but usually this opening seals off early in the presence of inflammation. The area is but feebly shut off from the left anterior subphrenic space. This space lies at a lower level and is not strictly posterior to the right anterior intraperitoneal space. It is certainly more descriptive to speak of it as the right kidney pouch (Morison) or the subhepatic fossa (Cantlie).

The left anterior intraperitoneal space occupies the so-called dome of the stomach's chamber, and an abscess in this area is often spoken of as perigastric or perisplenic. It is bounded above by the diaphragm; medially (right) by the left lobe of the liver, the falciform ligament

and the reflection of peritoneum forming the gastrohepatic ligament; laterally (left) by the spleen, the gastrosplenic ligament, and the abdominal wall, and extends as far back as the left lateral ligament of the liver. Adhesions of the anterior surface of the stomach and great omentum to the abdominal wall limit it below if an abscess forms. The floor of the space is formed by the anterior surface of the cardiac end of the stomach, the spleen, the left kidney, the adrenal, and the tail of the pancreas. The boundaries of this space are extremely variable. It is but lightly shut off medially from the right posterior intraperitoneal space and laterally is continuous with the left lumbar fossa or paracolic groove. It is the true subphrenic space on the left.

The left posterior intraperitoneal space is merely that contained in the lesser sac of peritoneum. The liver, lesser omentum, and posterior wall of the stomach bound it anteriorly; the left crus of the diaphragm, the pancreas, and the upper part of the left kidney and suprarenal bound it posteriorly. Laterally there is one surface of the spleen, below is the transverse colon, and medially or to the right is the duodenum and the hepatic artery, portal vein, and bile ducts with the posterior surface of a gastrohepatic fold of peritoneum, forming the anterior wall of the foramen of Winslow, through which the space connects with the right posterior intraperitoneal space. This cavity is not directly posterior to the left anterior intraperitoneal space, and it is more descriptive to speak of it as an abscess in the lesser sac.

ETIOLOGY

Subphrenic abscesses are due to many causes, and the location of the abscess or abscesses depends usually on the primary etiologic factor. The abscess may result from direct infection or soiling, or from a pyogenic infection borne to the area from a focus elsewhere. Approximately two-thirds are the result of soiling from a viscus within the abdomen, either before or following operation; one-sixth are the result of extension from an adjacent abscess (such as a perinephritic abscess); and one-sixth are the result of distant foci of infection. A high percentage of these abscesses follow an abdominal operation. Undoubtedly gravity plays an important part in the selection of one of the subphrenic spaces for the development of an abscess, particularly post-operatively. In an examination of the abdomen the posterior abdom-

inal wall is seen to be divided by the vertebræ into two deep gutters. These are divided transversely into the subphrenic pouches above, and are separated by the muscles of the loin, the kidney, and the pararenal fat from the pelvic cavity below. If a patient is confined to bed by any condition which produces fluid within the peritoneal cavity, and is not in the partial sitting posture, fluid tends to accumulate in the subphrenic areas instead of flowing down over the lumbar elevations into the pelvis where absorption is not so rapid, where abscesses are not so prone to develop, and where, if they do develop, they can be more easily dealt with, at least in the female. Undoubtedly, subphrenic abscesses are more common in males than in females, possibly because the anatomic variations between the pelvis of the male and female allows the paracolic grooves to drain more readily into the pelvis of the female than the male. In 113 patients observed in the Clinic eighty-four were males and twenty-nine were females.

Subphrenic abscesses are due to the perforation of a hollow viscus within the abdomen, such as perforating gastric ulcer or duodenal ulcer, appendicitis, infected gallbladder, abscess of the liver, kidney, spleen or pancreas, traumatism, periesophageal suppuration, degenerating carcinoma, infected spinal abscess, affections of the ribs, pyemia, pneumonia, empyema, lung abscess and distant foci of infection, such as carbuncles, cellulitis, and so forth.

With the suspensory ligament as the dividing line abscesses of hepatic, appendical, or duodenal origin usually form to the right; those from perforation of the stomach or infections of the spleen and pancreas are to be found to the left. It is surprising, however, that so many left-sided abscesses are of appendical origin.

Perforating ulcers of the anterior wall and greater curvature of the stomach are more likely to cause localized or general peritonitis than those of the lesser curvature and posterior surface, which tend to the formation of subphrenic abscess. In seventy-six cases reported by Barnard, twenty-one were due to gastric ulcer and five to duodenal ulcer. Among 252 cases reported by Finkelstein, sixty-seven (26.6 per cent) were due to lesions of the stomach. Of 100 cases in the Clinic, in which the etiology was fairly definite, there were three due to carcinoma of the stomach, nine to gastric ulcer, and ten to duodenal ulcer (Table 1).

Subphrenic abscess is too commonly of appendical origin. It occurs usually in a gangrenous, retrocecal, or highly placed appendix. Un-

TABLE 1
PRIMARY LESIONS

	Cases.	Stomach.	Duo- de- num.	Liver and gall- bladder.	Tho- rax.	Appendix.	Focal.
Barnard,.....	76	21	5	15	9	12	
Mayo Clinic.....	100	12	10	33	..	22	16
Finkelstein.....	252	67 (26.6 per cent)					
Lance.....	943		..	..	..	222	
Piquand.....	890		..	..	..	191	
Maydl.....	179	20 per cent	..	..	..	50 (23.3 per cent)	
Perutz.....	214	70 (32.7 per cent)					
Cases collected by Archibald.....	448		..	..	18		

TABLE 2
SUBPHRENIC ABSCESS OF APPENDICAL ORIGIN

	Cases.
Collected.....	{ 20 primary or pre-operative 17 early postoperative 3 late postoperative
Sonnenberg's Clinic.....	9 (of 600 cases of appendicitis)
Ross.....	30 (0.8 per cent of 3,391 cases of appendicitis)
Treves.....	6 (of 1,000 cases of appendicitis)
Kelly and Hurdon.....	7 (in 410 consecutive necropsies)
Subphrenic abscess develops in 0.6 to 1 per cent of all cases of appendicitis.	

doubtedly, it was a more common sequela of acute appendicitis when patients did not come to operation as early as they do now and when drainage was more generally practised, and especially in patients in whom drainage merely was instituted, and the appendix left to be removed later (Table 2). The mode of the spread of infection to subphrenic areas is by:

1. Direct extension by gravitation from a general or adjacent localized peritonitis.
2. Direct extension from the lower peritoneal fossa (pelvic cavity).
3. The portal vein.

4. Lymphatics:

- (a) From the right retroperitoneal cellular tissue.
- (b) From around the deep epigastric artery to the falciform ligament (Barnard). The lymphatics of the appendix, those of the ileocolic juncture, and those of the ascending colon are closely associated.
- (c) From the subphrenic lymph plexus which communicates through the lymph vessels which pierce the diaphragm, with the subpleural plexus on its superior surface; thereby with pus under tension infection may spread in either way (Fig. 262).

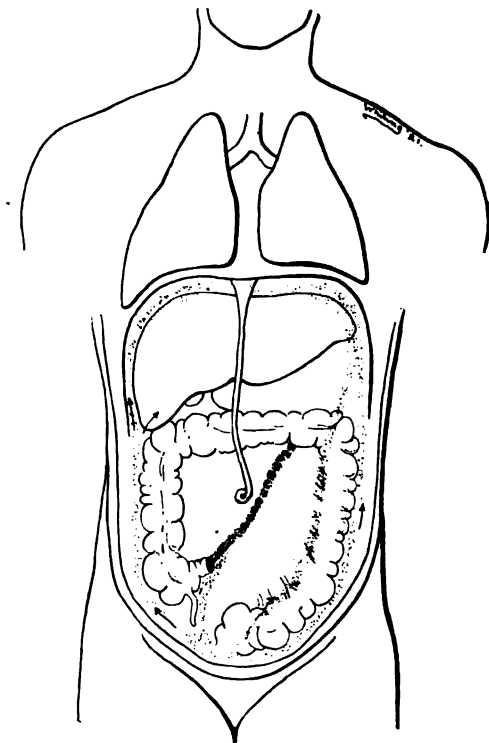


FIG. 262.—Diagrammatic illustration of lymph channels.

5. General infection through the blood stream.

The organisms usually found in subphrenic abscesses are *Bacillus coli* associated frequently with streptococci or various types of anaërobes.

The content of a subphrenic abscess varies with the etiology and

may consist of caseous debris, bile, liver cells, echinococcus cysts, carious bone, and occasionally of gastric or duodenal contents.

The pathologic process is infection, liquefaction, necrosis, and pus, the reaction forming a granulating protective tissue barrier. It requires apparently about two weeks for the abscess to wall off, therefore earlier transpleural drainage should not be considered. Usually the perforation in the wall of the stomach or duodenum closes spontaneously with the development of the abscess, and permanent fistula is rare. Gas, which is present in approximately one-third of all cases, is due either to an anaërobic infection or, more rarely, to direct connection from intestine or stomach. The abscess may be unilocular or multilocular.

SYMPTOMS

The symptoms of subphrenic abscess vary with the etiology, with the location of the abscess, and with the general resistance of the patient. They also vary with the onset of the disease, whether it is acute, insidious, or insidious with an acute exacerbation.

As the condition, in more than two-thirds of the cases, follows an abdominal operation, it should be suspected at once in a patient who maintains, for no obvious reason, an elevation of temperature and pulse after such an operation.

A long history of duodenal ulcer or gastric ulcer, repeated attacks of cholecystitis or of appendicitis should lead to the suspicion of abscess in unoperated cases. The most constant symptoms are:

Varying degrees of temperature, usually showing a marked variation (the church steeple type), with a corresponding increase in the pulse rate. The respiratory rate rarely follows the temperature pulse and the temperature and pulse curves, especially if associated with a chill, are practically always diagnostic of inflammation around the diaphragmatic level (Figs. 263, 264, and 265).

Pain at the costal margin referred also to the back and frequently to the shoulder area. Deep pain can usually be elicited by pressure over the costal margin from the front to the back or from side to side.

The leukocyte count varies; it is usually high in acute cases. Occasionally a leukopenia is found, and in such cases the abscesses are of the insidious type, and had formed some time before the patients came under observation, or, in a small percentage of cases, when the patients were in an advanced state of emaciation and generally lowered resistance. Sweating occurs. Rigors are common at some stages. A short catchy

diaphragmatic cough is often present. Dyspnea is observed occasionally. Vomiting and hiccup occur at some stage in about 50 per cent of the cases. Emaciation and weight loss is progressive in practically all cases. Inspection in approximately 60 per cent of the cases reveals a mass or bulging either in front laterally, or posteriorly at the trans-costal plane. The abdominal thoracic movement is usually limited on

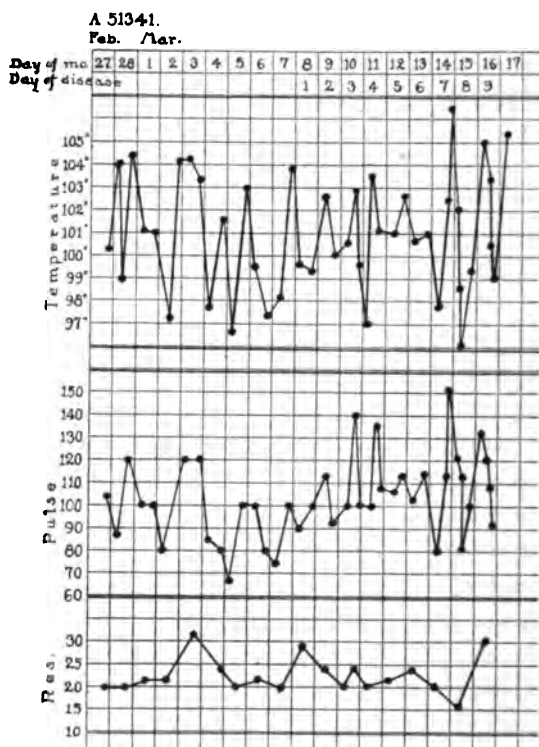


FIG. 263 (Case A51341).—Subphrenic abscess following cholecystostomy. Acute course in a very acute exacerbation and death. Note the very high temperature with accompanying pulse.

the affected side, and particularly in the early cases the interspaces directly over the abscess are frequently retracted. The latter sign is valuable in the early questionable cases. Further physical examination reveals a limitation of the diaphragmatic excursion, and some elevation on the affected side. The liver may be pushed down, and the stomach may be displaced downward or forward. Very often there are signs suggestive of a basal intrathoracic involvement, such as

dulness on percussion, and diminished breath sound and fremitus. Occasionally pleural friction sounds are heard; they are probably present in all cases at some time during the development of the abscess, but are not always recognized, since the pleuritis or perihepatitis resolves speedily. Careful physical examination reveals a different picture as the abscess develops. The friction rub may persist or disappear. As

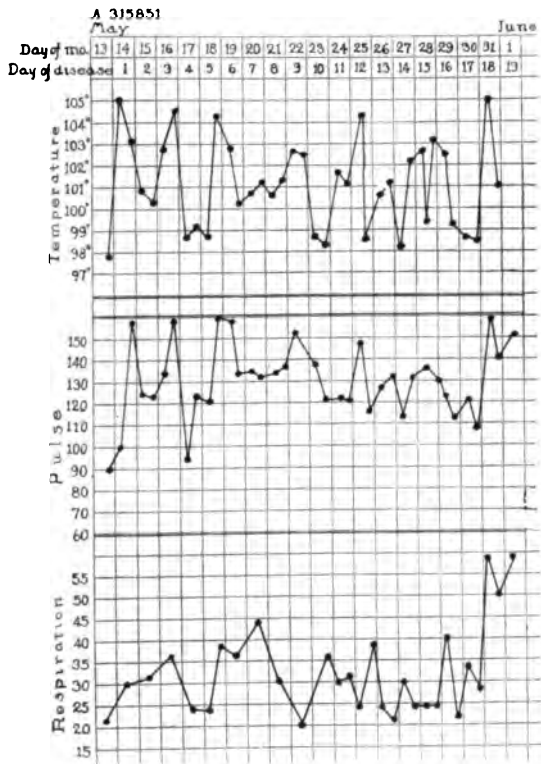


FIG. 264 (Case A315851).—Subphrenic abscess following empyema. Note the marked variation in temperature, pulse, and respiration with infection localized in diaphragm in this case, above and below.

the abscess extends there is an increasing area of dulness, and in percussing down the back normal resonance is usually elicited, then increasing dulness due to compression of the lung only; then dulness due to a collection of pus, or, if there is gas in the abscess, a variable area of hyporesonance, and then absolute dulness that may or may not merge into the liver dulness. At times there is a coin sound over the stomach

that is transmitted through the abscess to the dull area. The succussion splash, or bruit d'airain, may be heard over the area of hyperresonance if the patient is rolled from side to side.

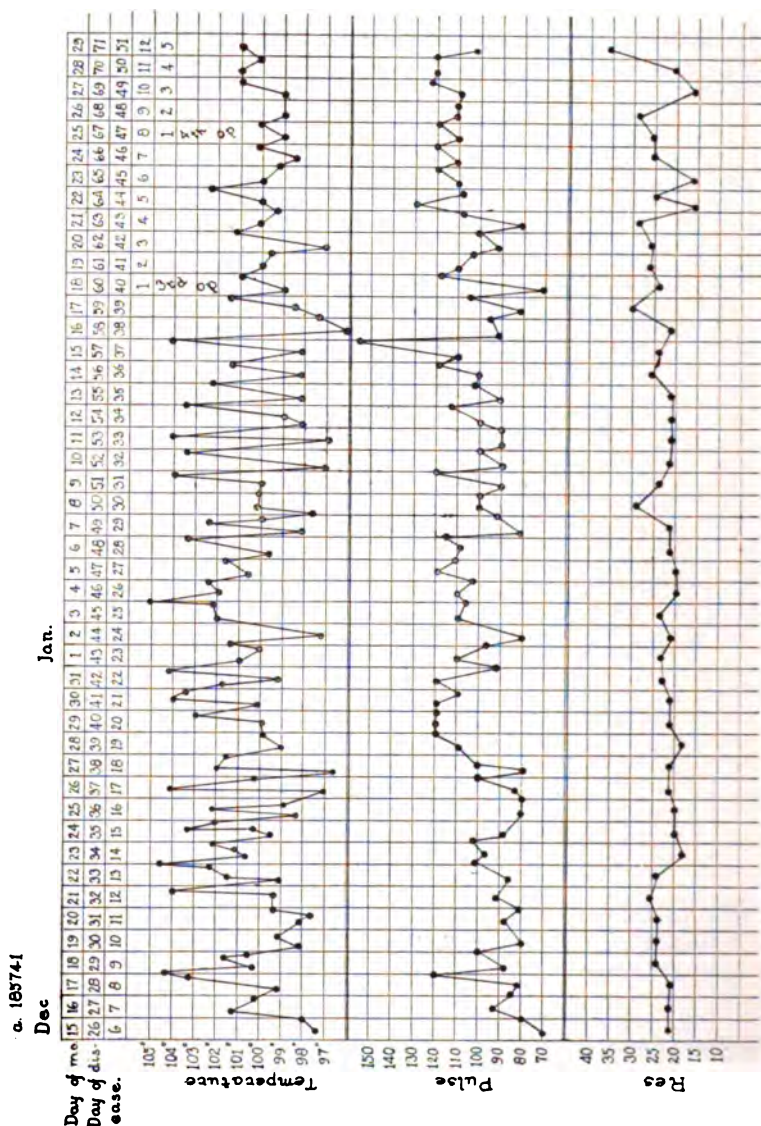


FIG. 265 (Case A185741).—Subphrenic abscess following drainage of appendical abscess. Note the very long course of disease, seventy-one days, with high temperature, but little respiratory change; eventual recovery.

Although the presence of gas in suphrenic abscesses was recognized by Barlow, and although Fagge had described it, it was not until von

Leyden published his classical paper on "Subphrenic pyopneumothorax abscess" (1880) that it was generally recognized.

ROENTGEN-RAY FINDINGS

Probably the most valuable aid in the diagnosis of subphrenic abscess is the roentgen ray. In early cases, or in extraperitoneal abscess, or in right posterior intraperitoneal abscess the diaphragm may be only slightly elevated, but may show a fairly characteristic irregularity. On the other hand, the diaphragm may be as high as the third or



FIG. 266 (Case A192433).—Subdiaphragmatic abscess.

fourth space and absolutely regular in outline. In the usual picture the diaphragm is raised to the fourth space, and shows some cupping. The lung is not collapsed, but is merely pushed up. The outline of the diaphragm is more uniform than in cases in which the diaphragm is elevated by an abscess of the liver. The line of the diaphragm is more irregular when it has been caught up by an old pleuritis or by a partial collapse of the lung. Gas can usually be discovered by the roentgenogram, and gas and fluid by the fluoroscope. With fluid in the pleural cavity the diaphragm is usually low; it is irregularly high from an early pleuritis, and the fluid is a later development. In such cases,

however, the costophrenic angle is generally blotted out, whereas in subphrenic abscess one or both angles are often clear. The degree of movement of the diaphragm can be accurately determined only by the fluoroscope. Full-sized stereoscopic plates and thorough fluoroscopic examination are essential in the diagnosis of these cases (Figs. 266 and 267).

The differential diagnosis of subphrenic abscess usually lies between pleurisy with effusion and abscess of the liver, but perinephritic abscess, hypernephroma, cysts, and aneurysm of the lower thoracic or upper abdominal aorta must also be considered. The clinical history of the



FIG. 267 (Case A324430).—Subdiaphragmatic abscess.

condition is the most valuable feature in the differential diagnosis. The carefully taken history, the roentgen-ray findings, and exploration with the needle should clearly determine the site of the abscess. However, certain factors help to differentiate subphrenic abscess, pleurisy with effusion, and abscess of the liver (Table 3).

It is not an easy matter, before operation, to determine the exact site of the abscess. Certain of the symptoms are common to all subphrenic abscesses, but others should clearly suggest the localization of the infection. Pain varies with the position of the abscess. Epigastric pain with bulging or a palpable mass in the epigastrium points to a

TABLE 3

FACTORS DIFFERENTIATING SUBPHRENIC ABSCESS, PLEURISY WITH EFFUSION, AND ABSCESS OF THE LIVER

Subphrenic abscess.	Pleurisy with effusion.	Abscess of the liver.
Postoperative abdominal sequelæ, or prolonged intra-abdominal or inflammatory focus elsewhere.	More common following influenza, pneumonia, exposure to colds, and so forth.	A history of dysentery (amebic). Usually blood infection.
Temperature of church steeple type, associated with rigors and sweating.	Temperature may be high at first, also with rigors, but not so often of the church steeple type, and the respirations are usually rapid.	Temperature and pulse curve much the same during the suppuration stage, but not early in the disease. Respiration not often increased.
Breath sounds well into the dull or tympanitic area of the abscess.	Breath sounds cease abruptly.	Less marked extension of dullness upward.
Little variation in the fluid level, unless gas is present; then usually succussion splash.	Level varies with the position of the patient.	
Heart rarely displaced. Dyspnea and cyanosis rare.	Heart frequently displaced. Dyspnea and cyanosis common.	
Liver usually pushed down without being enlarged.	Occasionally rotated downward and outward.	Liver enlarged and tender.
Icterus occasionally when the abscess has ruptured through the liver capsule and into the bile canaliculi.	None.	Icterus not common, but a peculiar greenish-yellow tint to the skin.
Diaphragm high.	Diaphragm low.	Diaphragm may be high, but irregular.

left anterior or posterior subphrenic abscess, and an easily palpable mass in the epigastrium associated with pain is more commonly due to a left anterior intraperitoneal abscess than to a left posterior intraperitoneal abscess. Bulging from the middle axillary plane forward along the subcostal plane is more common with a right anterior intraperitoneal than with a right posterior intraperitoneal or a right extraperitoneal abscess. The pain accompanying the right posterior intraperitoneal abscess is deep, and more of an ache, and the pain with a right or left extraperitoneal abscess is usually more acute and the area over it is more tender than with intraperitoneal abscess. The febrile reaction is usually not so acute in the extraperitoneal types as in the

intraperitoneal, also, the leukocytosis is not so high. Focal infections and lesions of the kidney more often produce extraperitoneal than intraperitoneal abscesses, whereas intraperitoneal abscesses usually come from an intra-abdominal cause.

The position of the liver is not altered by a left extraperitoneal abscess and often not greatly altered by a right extraperitoneal abscess. The right anterior intraperitoneal abscess usually pushes the liver down, whereas the right posterior intraperitoneal abscess may not greatly alter the position of the liver and may even push it up. The etiology, the nature and location of the pain, the tenderness, and the position of a mass serve fairly clearly to determine the position of the abscess. In considering the location it must, as previously pointed out, be borne in mind that with the suspensory ligament as the dividing line, abscess of hepatic, appendical, or duodenal origin usually forms to the right, and one from perforation of the stomach or from infection of the spleen and pancreas forms to the left. Although the majority of these abscesses are probably single at first, frequently in late cases they are multiple, and a single abscess is very often multilocular.

COURSE AND COMPLICATIONS

The abscesses may resolve, or may burst into the lungs, into the pericardium, into the stomach and be vomited, into the colon or duodenum and be evacuated in the stool, or through the skin anteriorly; or they may perforate into the retroperitoneal tissue and burrow extensively, even reaching the posterior culdesac in the pelvis.

It is difficult to know what percentage of subphrenic abscesses resolve and absorb. This resolution may occur early in certain cases that are in the more or less potential abscess formation stage. In those that have developed sufficiently to be recognized by the general group of symptoms, resolution and absorption are rarely seen. Thoracic complications, such as pleurisy, empyema, abscess of the lung, bronchial fistula, pericarditis, mediastinitis, and so forth, develop in a fairly high percentage of protracted cases. In fifty-six of seventy-six of Barnard's cases there were thoracic signs, and in 140 of 173 cases (82 per cent) collected by Lang.

Rupture of the abscess through the diaphragm into the lung is not uncommon. Within the last year I have seen one following a gastric ulcer that perforated through the diaphragm into the lung. The

contents were spat up and the patient recovered without interference. I have seen one case recently in which bilateral subphrenic abscesses, both apparently extraperitoneal, ruptured through the diaphragm on both sides into the lungs, and the contents were spat up. A third case was observed in which a subphrenic abscess, due to a degenerating hydatid cyst of the liver, also ruptured through the diaphragm into the bronchus, and pus with small daughter cysts in it was spat up.

Although rupture into the stomach is fairly common, rupture into the intestine is rare. This can readily be understood as the intestine seldom comes in contact with the abscess, either the stomach or liver intervening. The dread of those abscesses rupturing into the general peritoneal cavity and "lighting up" peritonitis is unwarranted, as this is extraordinarily rare.

On the whole, in less than one-third of the neglected cases the abscesses either resolve or open spontaneously. Death occurs from toxemia and general weakness and inanition.

PROGNOSIS AND MORTALITY

The prognosis in these cases must be guarded, and this again depends on the duration of the abscess, the etiology, the location, and the general resistance of the patient. Between 85 and 100 per cent of all patients not operated on die. Death has been reported in approximately 56 per cent of all patients operated on and not operated on. From 23 to 40 per cent of those operated on have died. The mortality rate should be approximately 16 per cent. A small percentage have died during operation or within a few hours after, probably because of extreme weakness before coming to operation. The greater number of deaths after operation, however, have been due to incomplete drainage of the abscess. A certain percentage of deaths is inevitable because the patient with this type of disease frequently comes to the surgeon too late, and in spite of complete drainage of the abscess the general infection causes death.

Careful necropsies and a study of necropsy findings have established beyond doubt that in the great majority of fatal cases, in which operation was performed, drainage was incomplete. At operation there has not been sufficient exposure of the abscess to reach all its ramifications. Very often a second abscess has been entirely overlooked; not infrequently the abscess was not located at operation (Table 4).

TABLE 4
MORTALITY IN GROUPS OF CASES OF SUBPHRENIC ABSCESS

	Patients with subphrenic abscess.	Patients operated on.	Deaths.	Patients not operated on.	Deaths.
Barnard.....	76	64 (73 operations)	24 (37.5 per cent)	12	12
Michel and Gross...	44	19	9 (47.3 per cent)	25	25
Eisendrath.....	106	84	23 (27.3 per cent)	22	18 (82 per cent)
Sachs.....	15.3 per cent... 50 per cent...	during first three weeks... after first three weeks.....	37.5 per cent		
Lang.....	176	52.1 per cent		87.7 per cent	
Maydl.....		35.7 per cent	56 per cent		
Elsberg.....		22 per cent	40 per cent		
Sonnenberg.....			42 per cent		
Mayo Clinic.....	113	81	27 (33.3 per cent)	32	31 (96.8 per cent)

TREATMENT

The treatment of subphrenic abscess, when recognized, has been operative. The operation generally practised has been either transpleural, with resection of the eighth, ninth, or tenth ribs, or the surgeon has approached the abscess by an abdominal incision. The abdominal route is necessary for the left anterior intraperitoneal abscess and for the left posterior intraperitoneal abscess, but the latter should be approached only from in front and drainage should be established from behind.

The extraperitoneal abscesses and both right intraperitoneal abscesses can best be dealt with through a lateral thoracic incision. There are certain objections to the old operation of rib resection, namely, unnecessary mutilation of the bony wall of the chest and tying off intercostal vessels, injury to the intercostal nerves, and so forth. Few surgeons are bold enough to take out sufficient rib (from 10 to 15 cm.) to permit thorough inspection of the subphrenic spaces, or to allow thorough and complete drainage subsequently. Osteomyelitis and periostitis frequently develop in the remaining portions of the rib, establishing chronic fistulas which are usually extremely difficult to cure by any means. Particularly in well developed and fleshy patients the ordinary incision exposes large fresh muscle surfaces and fascial planes and fat for the absorption of the pus. Many of these patients show an intense reaction to this source of toxic absorption.

In view of the foregoing objections to the old operation, and particularly since the cause of death is, as stated, incomplete drainage, or the overlooking of other abscesses, I have employed for five years, in abscesses located on the right side, the operation which in detail is as follows:

TECHNIC OF OPERATION

After the abscess has been located as accurately as possible, the height of the diaphragm and the extent of its lateral attachment are noted; the incision is planned for either the ninth, tenth, or eleventh

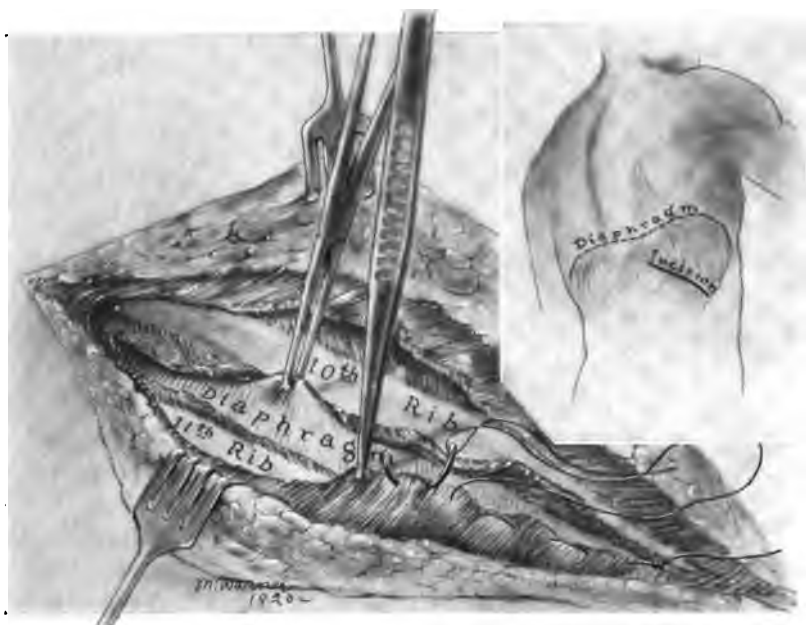


FIG. 268.—Suturing of the muscles to the diaphragm. The incision is in the tenth interspace.

right intercostal space. The patient is given one ampule of pantopon and scopolamin one and a half hours before operation and one-half of an ampule of pantopon (Roche) forty-five minutes later. Paravertebral anesthesia with 1 per cent novocain is employed and the nerves are injected two spaces above and below the space to be incised. Gas and oxygen are at hand if the patient unduly complains during the manipulations within the abscess. An incision is made in the skin, from 16 to 20 cm. in length, directly over the interspace and over

the area of bulging, if present; otherwise it extends from the middle or posterior axillary line forward. The skin is undermined for from 3.75 to 5 cm. back from the incision. The incision through the intercostal muscles passes about 1 cm. above the upper border of the lower rib, so that no intercostal vessels or nerves are involved. The parietal pleura with the diaphragm firmly adherent to it is separated from the rib above and from the rib below the incision. A spreading retractor is then inserted and the interspace is forced open sufficiently freely to admit the hand. The retractor is then withdrawn and the cut edge of the muscle with the pleura is sutured to the diaphragm with chromic catgut, the diaphragm is brought out as far as possible through the interspace with suitable traction forceps (Figs. 268 and 269).

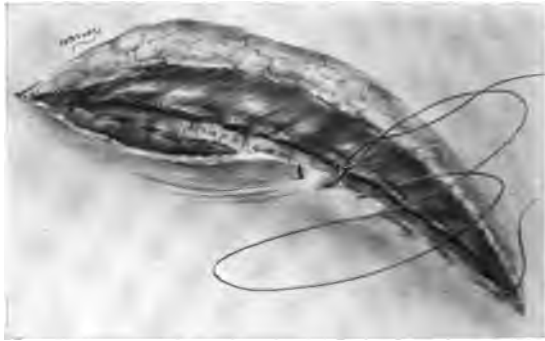


FIG. 269.—Suturing the skin over the cut muscle edge to the diaphragm.

The skin, which has been freely undermined, is then sutured to the diaphragm with catgut, over the first layer of sutures, so as to shut off completely the intermuscular and fascial planes. The patient may then, if preferred, be sent back to bed and the diaphragm be opened in from twenty-four to thirty-six hours, when the muscles and skin have become completely adherent to the diaphragm, or the diaphragm can be incised at once (Figs. 270 and 271).

In the majority of cases, after smearing the suture line with sterile vaselin, it is safe to open the diaphragm at once. After the diaphragm is opened sufficiently to admit the hand it should first be ascertained that the general peritoneal cavity is walled off completely from the abscess (it usually is); the liver, the stomach, the transverse colon, and omentum, as a rule, completely wall off the abscess. Care should be taken not to destroy these adhesions. After carefully clearing out



FIG. 270.—Retraction of diaphragm showing space between it and the liver.



FIG. 271.—Opening in the diaphragm.

all the abscess area and swabbing the cavity dry, a piece of iodoform gauze is packed along the adhesions, separating off the general peri-

toneal cavity, and a small separate piece is packed over the posterior angle of the incision to promote granulation and protect that angle from breaking through into the thorax. A lighted retractor is used carefully to inspect the entire abscess in order to avoid overlooking a pocket of a second abscess. The parts are palpated to make sure that there is not an underlying liver abscess. Finally the cavity is swabbed with ether and a two-way catheter drain wrapped with iodoform gauze is placed so that it reaches the deepest part of the abscess cavity. The adjacent skin edges are draped with vaselin gauze. The patient is returned to bed and placed in a half-sitting posture inclined to the right. The long end of the two-way drain protrudes through the dressing, and one ounce of saline is passed through the tube three times a day to clear it for drainage. On the second day the dressing is changed down to the vaselin gauze, which is not disturbed. On about the sixth or eighth day the patient is returned to the operating room, gas is administered if necessary, and the drain and all the packing are removed. The cavity is thoroughly swabbed with saline and inspected, employing a lighted retractor. The wound is packed with glycerin and saline (5 per cent), and a shorter two-way catheter is left in position until the cavity is gradually closed. As early as possible the edges of the incision are drawn together with adhesive strips. Too frequent changing of the deep dressing should be avoided; it serves only to destroy the young granulation and to excite an increase of temperature. Forced feeding, alkalization (120 grains sodium bicarbonate every twenty-four hours), glucose, and fresh air help to restore the patient. In many of these cases in which the abscesses have been well walled off and thoroughly dealt with at the first operation, it has been possible to resort to partial secondary suture on the eighth or tenth day. The advantages of this operation are:

1. Unnecessary mutilation of the wall which is involved in rib resection is avoided, and the possibility of osteomyelitis and periostitis, so frequent a sequela of rib resection in the presence of pus, is also obviated.
2. Free exposure is made to allow easy access to subphrenic spaces.
3. The minimum of fresh tissue is exposed to reinfection.
4. Primary or secondary hemorrhage from intercostal vessels does not occur because the vessels are not approached, and hemorrhage from the diaphragm has been controlled by the double layer of sutures.
5. The prolonged painful dressing of a superficially granulating surface is avoided.

From a careful study of the literature and of the cases represented in the tables certain general conclusions seem warranted (Tables 5-13).

TABLE 5
EIGHTY-TWO CASES DIAGNOSED SUBPHRENIC ABSCESS

(Males 66, females 16).....	82
Males died.....	23
Females died.....	4
Longest time after operation, twenty months.	
Shortest time after operation, one day.	
Average time after operation, eighty-four days.	
Age less than 11.....	0
Age from 11 to 20.....	2
Age from 21 to 30.....	17
Age from 31 to 40.....	23
Age from 41 to 50.....	13
Age from 51 to 60.....	19
Age more than 60.....	8
Highest leukocyte count.....	47,700
Lowest leukocyte count.....	5,200
Average leukocyte count.....	17,300
Leukopenia (leukocytes below 8,000).....	4 cases
Marked variation in leukocyte count:	
Case A191574 (acute, one week).....	from 11,000 to 29,000
Case A262217 (time not given).....	from 9,000 to 26,000
Case A281706 (insidious onset).....	from 12,600 to 47,000
Case A309608 (in one and one-half years).....	from 9,400 to 21,000
Case A192433 (acute, ten days).....	from 15,400 to 34,800
Case A125446 (death in nine weeks).....	from 15,000 to 24,300
Highest weight loss.....	96 pounds
Lowest weight loss.....	10 pounds
Average weight loss.....	33 pounds
Average duration of symptoms, four and one-half months.	

TABLE 6
SUBDIAPHRAGMATIC ABSCESS FOUND AT NECROPSY: THIRTY-ONE CASES

Males.....	18	Leukocytosis:	
Females.....	13		
Age:			
Under 11.....	0		
11 to 20.....	1	Lowest count, 8,200	
21 to 30.....	0	Highest count, 42,000 (varied from 14,800; onset of disease insidious; patient died in thirty-nine days).	
31 to 40.....	5	Average count, 17,400	
41 to 50.....	8		
51 to 60.....	11	Time between final operation and death:	
Over 60.....	6	Shortest.....	9 days
	31	Longest.....	63 days
		Average.....	22 days

TABLE 7

ETIOLOGY IN EIGHTY-TWO CASES DIAGNOSED SUBPHRENIC ABSCESS

	Cases.
Diseased appendixes	19
Longest duration of symptoms, two years.	
Shortest duration of symptoms, six weeks.	
Average time of onset, ten months.	
Drained	11
Gangrenous, removed	2
Gangrenous, no operation	1
Diseased gallbladders	23
Longest duration of symptoms, three years.	
Shortest duration of symptoms, three weeks.	
Average time of onset, ten months.	
Empyema of gallbladder	3
Ruptured	4
Malignant	1
Perforated duodenal ulcers	6
Longest duration of symptoms, two years.	
Shortest duration of symptoms, two weeks.	
Average time of onset, five months.	
No operation	1
Gastric ulcers	6
Longest duration of symptoms, three years.	
Shortest duration of symptoms, six days.	
Average time of onset, ten months.	
Cancer of stomach (time of onset, three months)	1
Hydatid cyst (time of onset not given)	1
Colectomy (time of onset, four weeks)	1
Focal infections	12
Prostatectomy, one month before coming to Clinic	1
Tonsillectomy, followed by pyemia, six months before coming to Clinic	1
Amputated leg, gangrenous, time not given	1
Carbuncle, one month before coming to Clinic	1
Pneumonia with pleurisy, time not given	2
Influenza, three weeks to two years before coming to Clinic	3
Mediastinal abscess, three weeks before coming to Clinic	1
Abscess of abdominal wall following removal of bladder stone, two months before coming to Clinic	1
Perinephritic abscess, eight weeks before coming to Clinic	1
Miscellaneous (not clearly determined)	13

TABLE 8
ETIOLOGY IN THIRTY-ONE CASES

	Cases.		Cases.
Posterior gastro-enterostomies.....	6	Second-stage Kraske.....	1
4 duodenal ulcers.		Cecostomy for acute obstruction.	
2 gastric ulcers.		Mikulicz one month later.....	1
Pyloric resections (one patient had cholecystectomy for stones).....	2	Subacute retrocecal appendix.....	1
Nephrectomy (patient also had duodenal fistula).....	1	Empyema (abscess).....	1
Anterior Polya for gastric ulcer.....	1	Ascites (later splenectomy).....	1
Cholecystectomies.....	6	Burns, with multiple abscesses.....	1
1 patient had herniotomy and excision of duodenal ulcer.		Perforation of large bowel.....	1
4 patients had appendectomies.		Unresolved pneumonia.....	2
1 patient had posterior gastro-enterostomy.		Prostatectomy.....	1
Choledochotomies.....	4	Abscess of the appendix (patient had ruptured pus tube, with drainage). 1	
1 patient had cholecystectomy.			
1 patient had cholecystostomy and an acute condition of the appendix.			
1 patient had an acute condition of the appendix and a right salpingitis.			

Three patients had acute appendicitis with retrocecal abscesses that probably extended to produce right posterior intraperitoneal abscesses.

TABLE 9
OPERATIONS IN THE THIRTY-ONE CASES

	Cases.
Two operations (gastro-enterostomy followed in eight days by jejunostomy).....	6
Three operations.....	2
Operations for other conditions, without relief, subdiaphragmatic abscess overlooked.	6
Emergency cases, bad risks, patients died within from three to fourteen days.....	7

TABLE 10
ONSET IN THIRTY-ONE CASES

	Average time from onset to death, days.	Cases.
Insidious with acute exacerbation.....	18	10
Nine months' history, with perihepatic abscess followed by rupture of the colon in one, six months' history in one, seven months' history in one, twelve months' history in one.		
Acute.....	13	9
Insidious.....	33	12
History of eighteen months after ruptured pus tube in one, history of thirteen months after acute appendicitis or ruptured pus tube in one, history of four months following extensive burns on the arm in one.		

TABLE 11

APPROXIMATE POSITION OF ABSCESS IN EIGHTY-TWO CASES*

	Cases.
Right anterior intraperitoneal.....	10
Left anterior intraperitoneal.....	12
Right posterior intraperitoneal.....	16
Left posterior intraperitoneal.....	6
Right extraperitoneal.....	4
Left extraperitoneal.....	5
Location not clearly defined in reports.....	29
COMPLICATIONS	
Empyema (1 double).....	11
Mass.....	15†
Gas.....	5
Lung abscesses.....	3
Perforation of diaphragm.....	4
Liver abscesses.....	11
Operation with wrong diagnosis.....	4

* The exact positions were not stated in many cases.

† Mass or bulging noted in fifteen cases only, but undoubtedly was present in a much higher percentage. Same applies to gas.

TABLE 12

APPROXIMATE POSITION OF ABSCESS IN THIRTY-ONE CASES

	Cases.	Average time patient lived after operation, days.
Right anterior intraperitoneal (acute in three, insidious in three, insidious with acute exacerbation in three).....	9	19
Left anterior intraperitoneal (acute in one, insidious in five, insidious with acute exacerbation in four)..... Right anterior intraperitoneal in one, right posterior intraperitoneal in one, pelvic abscess in one.	10	25
Right posterior intraperitoneal (acute in three, insidious in two, insidious with acute exacerbation in one) ... Retrocecal and pelvic abscess in one.	6	15
Left posterior intraperitoneal (acute in two, insidious with acute exacerbation in one)..... Left extraperitoneal in one.	3	13
Right extraperitoneal (insidious in one).....	1	38
Left extraperitoneal (insidious in one, insidious with acute exacerbation in one)..... Right extraperitoneal in one.	2	21

TABLE 13

COMPLICATIONS IN THIRTY-ONE CASES

	Cases.
Perinephritic abscess (left extraperitoneal, with perforation of colon in one, right extraperitoneal, with perforation of duodenum in one, right and left extraperitoneal in one).....	3
Liver abscess (with multiple foci in two, with single focus in one).....	3
Lung abscess.....	2
Perforation of diaphragm.....	2
Empyema (bilateral in three, single in four).....	7
Pericarditis.....	2
General septicemia (clinical diagnosis).....	3
Peritonitis (varying amount of serofibrinous or fibrinopurulent exudate) . .	7

CONCLUSIONS

1. Subphrenic or subdiaphragmatic abscess is a grave condition and causes a high mortality. The convalescence of patients who recover is long, tedious, and accompanied by serious complications, such as renal and thoracic lesions which often leave the patient in chronic invalidism.

2. The serious sequelæ of the disease are due to the fact that the condition is not recognized sufficiently early, or is not dealt with promptly and completely.

3. The condition is secondary to infection elsewhere, and a high percentage of cases follows upper abdominal infection at operation or postoperatively.

4. Gravity accounts for the selection of the subphrenic area in the development of the abscesses following abdominal soiling.

5. Every effort should be made to prevent soiling of the subphrenic area during upper abdominal operations, and drainage, particularly of the upper abdomen, should be employed only when absolutely essential.

6. Subphrenic abscess should be suspected in all patients who, following abdominal operations, maintain, for no obvious reason, an elevation of temperature and pulse.

7. Roentgen rays should be employed as an early diagnostic aid.

8. Needling for diagnosis is a dangerous practice, and should be used only to rule out pleural effusions. The needle should not be passed through the diaphragm into the abscess until the patient is on the operating table, then, if pus is located, the needle should be left in position and the operation carried out without delay.

9. More deliberate and protracted operations can be performed with minimum risk to these emaciated and seriously ill patients under paravertebral anesthesia than under general anesthesia.

10. A wide exposure of the abscess area is necessary.
11. Efficient drainage must be secured.

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FRACTURES OF THE FEMUR: END RESULTS*

MELVIN S. HENDERSON

My part in this symposium is to discuss the end results of fractures of the femur. In order to gain the proper perspective I have reviewed the literature of the last five years and have carefully, with the assistance of Dr. J. I. Mitchell, studied the records of 222 consecutive cases in the Mayo Clinic. The literature on the subject is so abundant that I shall not attempt to discuss it, but proceed at once with the discussion of data concerning the patients who have been under our care.

Fifty-seven of the 222 patients had sustained fractures recently; the remaining 165 presented the end results of treatment which they had received elsewhere. These patients came to the Clinic because of malunion, delayed union, nonunion, chronic osteomyelitis, stiff joint, and so forth.

RECENT FRACTURES

Eighteen of the fifty-seven patients were under fifteen years of age. The data concerning patients who were not traced or under observation have been eliminated from the discussion since the end results were too indefinite. There were three deaths. One patient died of a fractured skull the day of the accident, two died postoperatively, one of pulmonary fat embolism, the day of the operation, and one, a woman, aged fifty years, died in the third week from pulmonary embolism following reduction and treatment by the Whitman method of a fracture of the neck of the femur. Necropsy disclosed a huge pulmonary embolism evidently having its origin in a thrombosis in the common iliac vein. Thus remain definite records of forty patients from which to estimate end results.

Nine patients had sustained fractures of the neck of the femur; seven were cured. One fracture was of the intertrochanteric type, and a satisfactory result was obtained. One was a frank failure owing, I

* Presented before the American Orthopædic Association, Boston, June, 1921. Reprinted from the *Journal of Orthopædic Surgery*, 1921, iii, 520-528.

believe, to improper reduction of the fracture. One patient failed to carry out the treatment.

The Whitman method of treatment was preferred, but when for some reason it could not be carried out, the Ruth Maxwell traction and countertraction method was employed with a certain amount of abduction. Countertraction, an essential part of this treatment, when properly applied, raises the trochanter and rotates the foot inward. It has been our practice, regardless of the type of fixation, to break down the impaction and set the fracture as any broken bone is set. On the whole, it is probably better routinely to break up a so-called impaction of a fractured hip except when for some reason, such as old age with debility, or a systemic terminal disease, such as pernicious anemia, malignancy, or tabes dorsalis, the treatment of the fracture must be carried along on palliative lines. There is no reason why a fracture of the neck of the femur either of the subcapital or the intertrochanteric type should fail to unite in persons in good health, and old age is not in itself unfavorable.

Seven patients had sustained fractures in the upper third of the femur; all obtained satisfactory results. Four were operated on and three were treated conservatively. Theoretically, owing to the slightly forward and outward displacement of the upper fragment, traction should be applied in a corresponding direction. The distance from the symphysis pubis to the adductor tubercle on the inner condyle is increased by more than 2 cm. when the hip is in full abduction. The powerful adductor magnus must, therefore, be stretched correspondingly. I believe this is sufficient reason why traction should not be made in this manner. Lee has mentioned this recently. Straight extension is sufficient if properly applied and not used as a mere ritual.

There were fifteen fractures in the middle third of the femur, with fifteen cures. Ten patients were operated on and five were treated conservatively. A slight angulation will not so easily cause a static arthritis in this area as at either end of the bone. Sagging of the lower fragment posteriorly and laterally may occur and care should be taken not to permit it to become too greatly displaced.

There were five fractures in the lower third, with three cures. One patient was operated on and four were treated conservatively. The lower fragment may become displaced posteriorly and the end press on the popliteal vessels and nerves. If the fracture is not readily reduced by manipulation one should not hesitate to reduce it by operation, for

if it is left but a short time reduction even by the open method may be very difficult.

In children the epiphysis may be separated and displaced forward. There were three fractures of this type in the series, with two satisfactory results. One of the patients who died was a boy of nine years, with an epiphyseal separation. He died the first day from pulmonary embolism. There were two open operations and one closed. It is astonishing how little deformity is evident in an epiphyseal separation with forward displacement, and it is not surprising that this somewhat unusual condition is often not recognized by the general practitioner. Acute flexion of the knee with traction and manipulation may reduce the deformity. If the reduction is difficult and open operation is decided on, the split patellar incision gives excellent exposure and enables the surgeon to replace the epiphysis accurately. Personally I have no hesitation in making a full exposure of the joint in this manner.

The problem of when to permit weight bearing is most important. The time varies with the type and location of the fracture and the age of the patient, but there should be a cardinal rule that patients with fractures of the femur should not be allowed to walk, when the time comes to permit weight bearing, without a Thomas caliper walking splint. The splint should be discarded only when the clinical and roentgen-ray examinations show firm union. I find that I am inclined to lengthen the period of restricted weight bearing rather than to shorten it.

Of the forty patients, thirty-five (87.5 per cent) were cured. Two had residual shortening and a consequent limp, and although they obtained excellent function, they are classified in the group of improved. The failures in the shaft were usually the result of bowing of the bones. This occurs even when the patient is wearing a cast. Some of the patients were permitted weight bearing without the walking caliper splint too soon, and some disregarded instructions.

Our practice now in treating recent fractures of the femur may be tersely described. The younger the patient, the easier is the application and the carrying out of conservative measures, although occasionally, even with babies, difficulty will be encountered in satisfactorily engaging the ends of the bone. When this occurs open operation should be resorted to. In vigorous adults under proper surroundings the open operation, using beef-bone plates, or if necessary metal plates, as internal fixation in my experience at least has been more satisfactory than

conservative measures. In a well equipped fracture ward in a hospital with trained attendants conservative measures would, I believe, give equally good functional results, but such ideal conditions are rarely at hand. The proper internal splinting and postoperative fixation insures a perfect anatomic result. A good fracture table is essential; every hospital should have one. In elderly patients I have been prone to resort to conservative measures, but in the future I believe I shall operate more often if patients are in good general health. This does not apply to patients with fractures of the neck of the femur, for which the Whitman abduction method gives perfect control of the fragments. Prolonged fixation in plaster tends to stiffen the knee and we are now putting joints in casts to permit early active motion of the knee.

OLD FRACTURES

Of the 165 patients who came to us for consultation because of faulty end results, fifty had had fractures of the neck of the femur, and all but six of the fifty were operated on. Five patients left our care too soon to show the end results. Thirty-nine of the traced patients were operated on and twenty-eight (71.7 per cent) were cured. In the successful cases an autogenous bone transplant was used for nonunion in eight, beef-bone screws in eight, and metal screws or nails in four. Two patients had malunion, and osteotomy was performed. In six the union was delayed and plaster-of-Paris casts were applied. There were no deaths, although a patient operated on recently, who was not included in the group, died three days after the operation because of cerebral embolism originating in a thrombosed common iliac vein. The thrombus passed through a patent foramen ovale, which had not caused symptoms during life. Plaster of Paris extending from the chest to the toes on the side involved and to the knee on the opposite leg affords firm fixation. On the affected side a joint may be made in the cast at the knee so that the knee may be moved gently and stiffness be prevented.

I have not sufficient time to permit a free discussion of the type of case that should be selected for the pegging operation, and the type for the Brackett operation. I may say, however, that if absorption of the neck is practically complete and the head lies flush with the margin of the acetabulum, a bone pegging operation, no matter how carefully performed, is useless. Roentgenographs should always be taken with the foot in eversion and in inversion to show the amount of neck

remaining. When a fair sized remnant of neck remains I prefer to use the fibula as a transplant on account of its size and strength, but when there is little or no neck I prefer the Brackett operation.

Transtrochanteric fractures and subtrochanteric fractures, as a rule, unite without any difficulty, but malunion may follow, necessitating an osteotomy. If the fragments are comminuted there may be excessive callus with some shortening, but strenuous attempts to obtain lengthening are not unattended with danger, for the muscles, nerves, vessels, and tendons may all be very much shortened. Even though there is considerable shortening, if union is firm and the weight-bearing line is satisfactory it is my opinion that no interference should be undertaken.

In treating old fractures of the shaft of the femur, whether in the upper, middle, or lower third, the problem is much the same. An operation is difficult and may be attended with infection and risk to life. It is difficult to estimate end results in such patients because a study should be made of individual cases, and because in some it would be absolutely impossible to obtain perfect results. I have arbitrarily classified as cured patients in whom we have attained what I consider the maximum of benefit for the individual, thus making the classification a personal equation. Therefore a discussion of some of the interesting facts I have elicited in the scrutiny and study of the histories of these patients may possibly be of more value than an attempt to tabulate results.

I was very much impressed by the fact that it is an extremely difficult matter to keep the records of patients who are under observation for some time in a manner so that an intelligent and comprehensive résumé of the patient's progress from the time he enters the hospital until he is dismissed cured, improved, unimproved, or still under observation can be made. An editorial in the March issue of the *Journal of Orthopædic Surgery* on the subject of reporting results in fractures briefly states what such a report should be. But few of us can really offer such valuable data.

The metal plate was used in fifty-eight operations. In this day of autogenous bone grafting this seems rank heresy, but I must confess that in many of these old fractures of the femur, after I have made a tediously long dissection to expose the fragments, freshen them, and fit the ends, I am only too glad to fall back on the metal plates and screws as the easiest and quickest way out of a difficult position. Prolongation of the operation to apply a bone graft is attended with a risk that cannot

be lightly considered. The oblique and spiral fractures may often be easily held with beef-bone screws alone, and in the transverse fractures the beef-bone plate and screws combined are in many respects ideal. Sepsis is more prone to follow the use of the metal plates than the use of the beef-bone plate or autogenous bone graft. It is now my practice to remove every metal plate as soon as union is sufficiently firm to permit its discontinuance. Infection may spoil a well conducted operation, and is a factor to be considered in dealing with end results. In the present series infection ran high and occasionally caused failure. We have classified as infections all cases in which pus discharged, regardless of whether or not it influenced the convalescence. Twenty per cent of the clean cases became infected. In the cases in which operations had previously been performed (in many infection had followed the primary operation), 43 per cent developed infection afterward. I do not believe this to be the fault of our technic, but rather the type of case, for in a recent investigation of 413 autogenous bone grafts, in 247 operations for ununited fractures infection developed in 10 per cent of the clean cases, and in 41.3 per cent of the previously infected cases there was a discharge of pus. In the easily conducted 166 spinal transplants of the series, however, only 2.6 per cent became infected in spite of the fact that two large incisions were made and the motor saw employed in each case. Under a system of close checking up on the postoperative condition of wounds following general surgical operations in the Mayo Clinic, Sistrunk finds that almost 10 per cent of the clean cases show some degree of infection.

Whatever the means taken to hold the fragments in position, some form of postoperative fixation is essential. There are two ways to secure this, one is fixation in a cast, and the other is some form of extension. I have no hesitation in saying that to rely on the cast to hold the fragments in place in a fracture of the shaft of the femur either recent or old, when there is any tension of the muscles and tendons, is to court disaster. Bowing may occur no matter how carefully a cast is applied, particularly if it is put on under extension on a fracture table. The only safe way is to put the patient in bed with enough extension to overcome the spasm of the powerful muscles. I prefer to apply a light cast to the thigh and a Thomas splint, elevate the foot of the bed, and by a combination of weights strung over a pulley and the patient's own weight maintain extension until the fracture is firmly enough united so that either a cast or a walking caliper may be used. In the

majority of instances adults should not be permitted full weight bearing for six months following operative measures.

There were 115 fractures of the shaft of the femur. Twenty-four were in the upper third; fifty-seven in the middle third, and thirty-four in the lower third. Ninety-eight patients were traced, seventeen were not traced. Sixty-nine were operated on by some form of open operation. In this list are the nonunions, malunions, and delayed unions, with fifty-three (76.7 per cent) satisfactory results. Twenty-nine patients were treated by conservative measures with twenty-seven (93.1 per cent) satisfactory results. The nonoperative treatment gave a greater number of proportionately good results than the operative treatment. It must be remembered, however, that operative measures were employed for the more serious fractures, while nonoperative measures, such as manipulations under ether to line up the fragments and treatment by extension and Thomas splints, were employed for the more simple fractures.

It is not possible to deduce the best method by statistics, but I believe that in fractures of the neck of the femur, if enough of the neck remains, the bone peg, preferably the fibula, is the method of choice, but if the neck is absorbed, the Brackett operation offers the most encouragement. In the shaft, theoretically, the bone graft, either the intramedullary, inlay, or massive, is preferable, but for practical reasons the metal plate must often be used. The beef-bone plate is supplanting the metal plate in our practice and I believe is much better tolerated by the tissues.

One hundred two operations were performed for old fractures with two deaths. One woman, aged thirty-eight years, with nonunion of the middle third of the femur, died the day of the operation, because of pulmonary embolism; necropsy was not permitted. One patient, a man aged thirty-two years, died the sixth day after operation and necropsy failed to disclose adequate cause for death. A slight bronchopneumonia and a slightly contracted kidney were found, but no evidence of pulmonary embolism. I am inclined to believe the patient died of renal insufficiency, although clinical examination had been negative.

There are two serious complications that are of clinical significance and which stand out in this review. First, thrombosis of the common iliac artery in fractures of the neck of the femur. This is, I believe, more common than we have thought. It was demonstrated at necropsy in two of our patients dying of embolism, and probably was the cause

of the persistent edema seen in some of our patients, who, so far as the fracture was concerned, obtained excellent results. Second, dilatation of the stomach. This occurs but rarely in orthopedic cases, but if it is unrecognized may cause the death of the patient. I have often heard Dr. C. H. Mayo say that if in the surgical wards of hospitals the interns carried stomach tubes hanging around their necks instead of stethoscopes the mortality rate would be reduced.

SUMMARY

Fifty-five of the fractures were recent; nine were in the neck of the femur, and seven were cured. The two failures were owing in one instance undoubtedly to improper reduction, and in the other to the removal of the cast in three weeks and the patient's refusal of further treatment. End results were observed in forty patients; thirty-five (87.5 per cent) had obtained entirely satisfactory results. Although I am not prepared to state, from such a small series of cases, whether open operation or conservative measures is the preferred treatment, I do not hesitate to operate on patients, providing conditions are satisfactory, if I am satisfied that the fragments are not in good position.

One hundred sixty-five of the fractures were old, or end results of fracture of the femur. It is difficult to judge the conditions under which the primary treatment was carried out, but it was undoubtedly quite inefficient in the greater number of cases. In the smaller number union had been slow and the pull of the powerful muscles or too early weight bearing had caused bowing. It is difficult to determine from the roentgenograms or from clinical examinations when union is complete in cases of malunion. On opening some of the fractures of this type motion was easily demonstrated. In fifty patients the causes of the disability were faulty end results following fracture of the neck of the femur. Five patients were not traced and six were not operated on by the open method; the remaining thirty-nine were operated on. Osteotomy for malunion was performed in two; the others were treated for nonunion, and twenty-eight (71.7 per cent) were cured. In cases in which the neck was absorbed and union was attempted by using a bone peg failures were uniform. A fair amount of neck must remain if there is to be any chance of union. The Brackett operation is the method of choice when the neck is destroyed.

One hundred fifteen patients with fractures of the shaft were treated and ninety-eight were traced. Sixty-nine patients were operated on

and 76.7 per cent were cured. Twenty-nine were treated by conservative measures and twenty-seven (93.1 per cent) obtained satisfactory results.

END RESULTS IN FRACTURES OF THE FEMUR, 222 CASES

57 recent fractures, 165 old fractures

40 patients with recent fractures traced, 35 (87.5 per cent) cured.

10 fractures were of the neck, 8 were cured.

7 fractures were of the upper third, 7 were cured.

15 fractures were of the middle third, 15 were cured.

5 fractures were of the lower third, 3 were cured.

3 were separations of the epiphysis, 2 were cured.

2 postoperative deaths, both due to pulmonary embolisms.

143 patients with old fractures were traced.

50 fractures were of the neck.

39 were operated on, 28 (71.7 per cent) were cured.

6 were manipulated and casts applied, 6 were cured.

5 patients were not traced.

115 fractures were of the shaft.

69 were operated on, 53 (76.7 per cent) were cured.

29 were not operated on, 27 (93.1 per cent) were cured.

17 patients were not traced.

POSTERIOR LATERAL INCISION FOR THE REMOVAL OF LOOSE BODIES FROM THE POSTERIOR COMPARTMENT OF THE KNEE JOINT*

MELVIN S. HENDERSON

Loose bodies are not infrequently present in the posterior compartment of the knee joint. Occasionally they may wander into the ante-

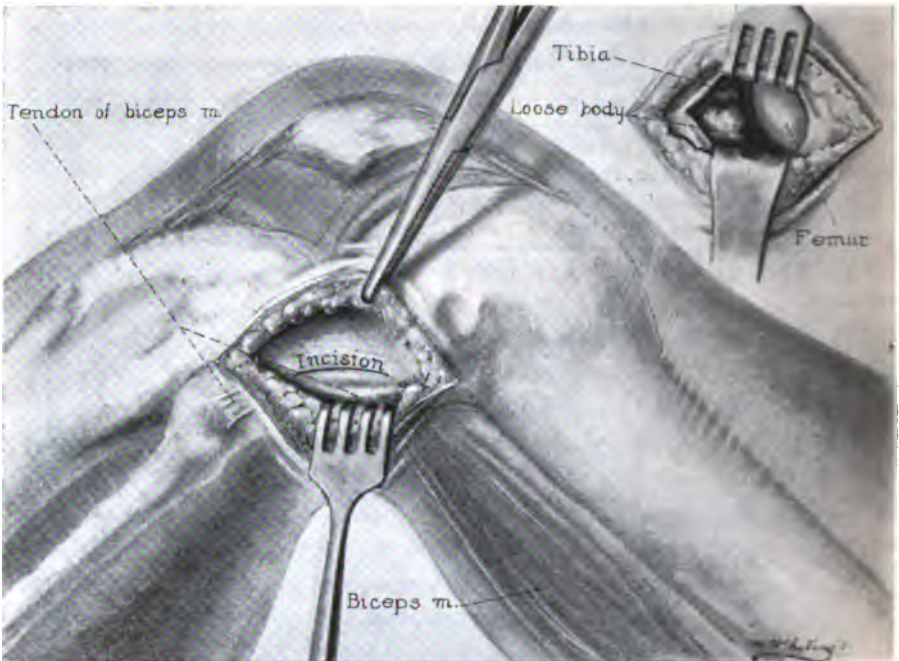


FIG. 272.—External posterior lateral incision. Insert shows loose body.

rior compartment and be readily accessible, but more often they are too large for this, and it is necessary to remove them through an incision that will permit access to the posterior compartment of the joint.

* Reprinted from *Surgery, Gynecology, and Obstetrics*, 1921, xxxiii, 698-699.

Brackett and Osgood, in 1911, described an incision through the popliteal space which is excellent, but entails careful dissection in order to avoid the popliteal vessels and nerves, and it is difficult to make, particularly in fleshy or muscular patients.

The posterior compartment of the knee joint is practically divided by a mesial septum into internal posterior and external posterior compartments. A posterior lateral incision is therefore often necessary on

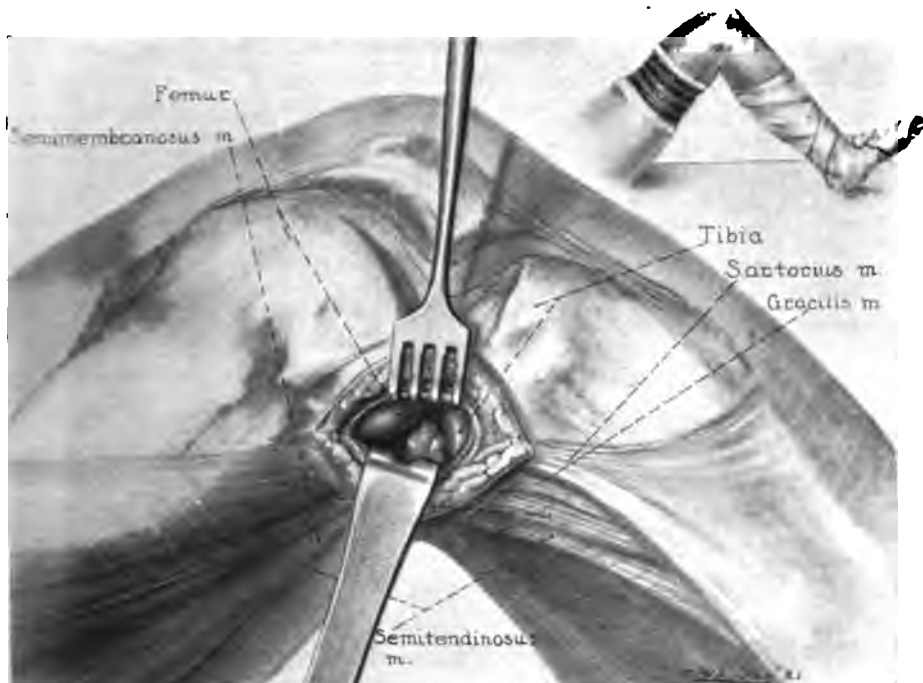


FIG. 273.—Internal posterior lateral incision. Insert shows knee flexed to the right angle, and the position of the leg on the operating table.

both sides in order that the exploration for the bodies may be completed, but both incisions are small and practically no dissection is needed.

The knee is prepared in the usual manner and a tourniquet applied. The foot of the table is not dropped as in explorations for semilunar cartilages, or in splitting the patella. The knee is flexed to a right angle, thus relaxing its posterior capsule. If the loose bodies are all in the outer division of the posterior compartment the incision should be made posteriorly, well on the outer side, but in front of the fibula

(Fig. 272). A semilunar incision with the convexity anteriorly or posteriorly may be made in the skin, and a straight incision parallel with the longitudinal axis of the leg made in the capsule. This may be enlarged and retractors placed to give an excellent view of the posterior cavity of the joint. A large curet or gallstone scoop may be used to explore and remove the loose bodies. The mesial septum prevents ready access to the inner compartment, and if exploration on that side is necessary, rather than to cause trauma to the interior of the joint by forcing an instrument through it, an incision similar to the one just described should be made on the inner side. This is anterior to the relaxed tendons of the semitendinosus, semimembranosus, sartorius, and gracilis muscles (Fig. 273) and gives ready access to the inner division of the posterior compartment. Plain catgut sutures are used to close the capsule and silkworm and dermal sutures to close the skin. Fixation in plaster of Paris or by splint is not necessary, although it may be employed for from twenty-four to forty-eight hours to prevent bleeding that may follow the involuntary movements of the patient on coming out of the anesthetic.

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SARCOMA OF THE LONG BONES; A STUDY OF MICROSCOPICALLY PROVED CASES*

HENRY W. MEYERDING

The successful treatment of sarcoma of the long bones depends on the early recognition and eradication of the growth and on the prevention of metastasis. The successful removal of sarcoma by local excision or by amputation has been repeatedly demonstrated. Pulmonary metastasis through the blood stream is the most common complication; however, this may not occur for years, the patient meanwhile remaining in good health. The roentgenogram affords our earliest means of diagnosis of metastasis, but, unfortunately, when metastasis has occurred the prognosis is hopeless.

That the problem of sarcoma of the long bones has not been solved is obvious from the reports in the literature. Increasing percentages of five-year cures are being reported in cases of carcinoma, the result of emphasis placed on early diagnosis, radical surgery, and preventive therapeutic measures, but reports of cures following the treatment of sarcoma remain most discouraging.

Future methods of treating sarcoma of the long bones may best be judged in relation to past methods and results. At a symposium on sarcoma of the long bones given before the Royal Society of Medicine in London in 1912, St. Bartholomew's Hospital reported sixty-one cases with three three-year cures, and St. Thomas' Hospital reported forty-five cases, with five three-year cures in cases of sarcoma of the giant cell type. Escher, in 1920, reported from the University of Vienna forty cases, with six patients living more than two years; Bloodgood, in 1920, reported eighty-nine cases, with four patients living five years; Coley, in 1919, reported 250 cases, with thirty-one patients living three years. In the Mayo Clinic from September, 1907 to September, 1921, 470 cases were diagnosed sarcoma of the extremities; 168 (35.7 per cent)

* Presented before the American College of Surgeons, Philadelphia, October 25, 1921. Reprinted from *Surgery, Gynecology and Obstetrics*, 1922, xxxiv, 321-332.

of these were sarcoma of the long bones. One hundred nine of the patients were operated on and a microscopic diagnosis was made of sarcoma of the femur, tibia, fibula, humerus, radius, and ulna. Besides the 470 cases, there were eighteen in which a diagnosis of giant cell tumor of the long bones was made at operation and from microscopic examination; these cases have not been included in the study, as we considered them benign (Figs. 274, 275, 276, and 277).

All of the 109 patients were subjected to careful history taking and physical and roentgenographic examinations. Routine examinations were made to exclude syphilis. Esmarch's bandage was applied to pre-



FIG. 274.—Foreign body giant-cell tumor. FIG. 275.—After excision and autogenous bone graft.

vent metastasis. The tumor was explored and a section examined microscopically before radical surgical measures were undertaken. Fifty-nine (35 per cent) of the 168 patients were inoperable at the time of examination or they refused operation. Usually a consultation was held of two surgeons and the examining physician before amputation or operation was decided on. In studying the cases, if any doubt existed with regard to the previous interpretation, the material in the pathologic museum was again examined microscopically by the consulting pathologist.

In eighty-five of the 109 cases the sarcoma was in a lower extremity.

It was in the femur in forty-nine; in the tibia in twenty-seven; in the fibula in nine; in the humerus in eighteen; in the radius in three; and

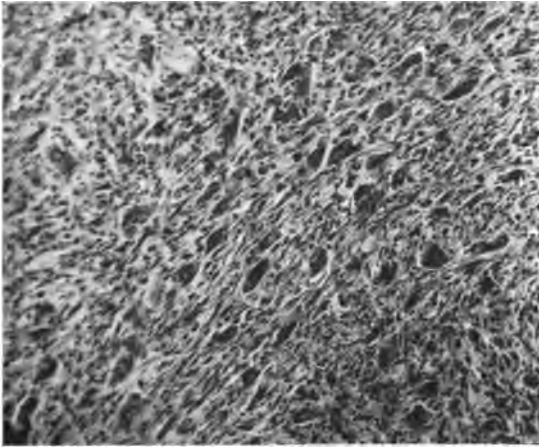


FIG. 276.—Typical giant-cell tumor containing numerous foreign body giant cells ($\times 100$).

in the ulna in three. The left femur was involved in twenty-seven, the right in twenty-two, the upper end of the left tibia in seventeen,

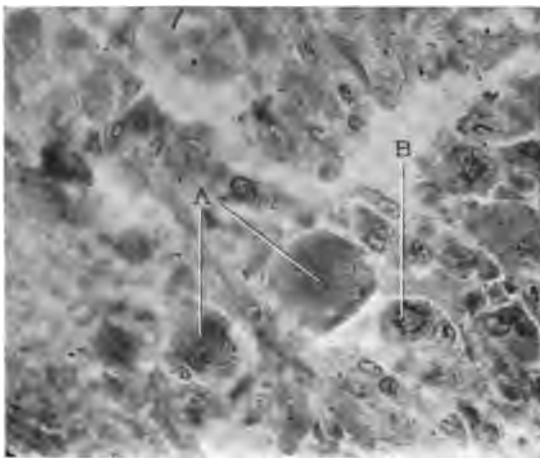


FIG. 277.—Medullary sarcoma of tibia containing tumor giant cells: *a*, Tumor giant cells; *b*, mitotic figure ($\times 500$).

and the right in ten. Figure 278 shows the distribution, location, and type of the tumor (Table 1).

The average age of the patients in the series was twenty-six and six-tenths years. Sixty-nine were males and forty were females. Twenty-

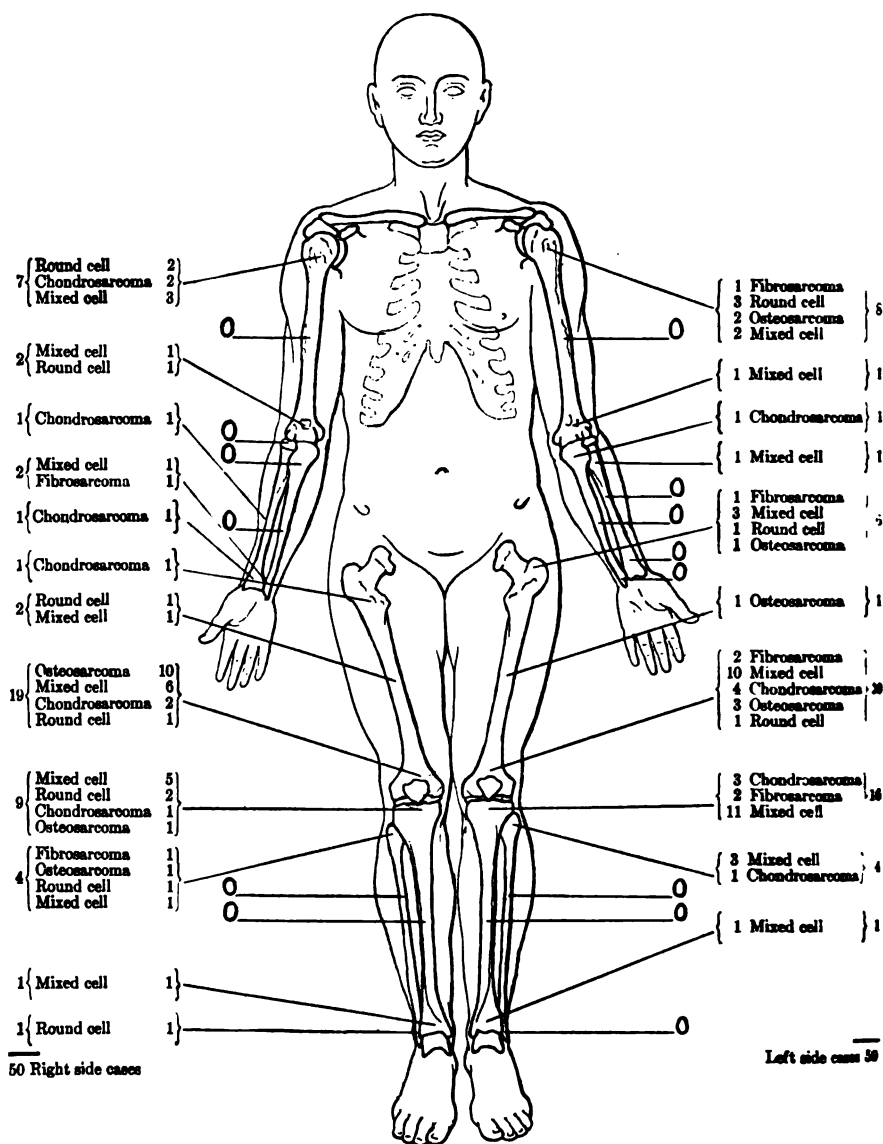


FIG. 278.—Type and distribution of sarcoma of the long bones.

seven of the males were more than thirty years; the oldest was sixty-nine years and the youngest nine. Thirteen of the females were more

TABLE 1

SARCOMA OF EXTREMITIES

470 Cases—September, 1907 to September, 1921

Long bones (upper 33; lower 135).....	168
Long bones operated on (upper 24; lower 85).....	109
Long bones not operated on (upper 9; lower 50).....	59
Small bones and soft tissue.....	302
Small bones and soft tissue operated on (upper 42; lower 113).....	155
Small bones and soft tissue not operated on (upper 56; lower 91).....	147
Eighteen cases of giant-cell tumors of the long bones are not included, since all the patients are living and the condition is considered benign.	

than thirty years; the oldest was sixty-seven years and the youngest four. In eighty-two (75.2 per cent) the common age of occurrence was between ten and forty years.

It is important to obtain a careful history with regard to pain, rapidity of the growth of the tumor, duration of symptoms, type of trauma, syphilis, disease of the bones, fractures, and previous treatment. The clinical history plays an important part in the differential diagnosis. Family history showed tuberculosis in nine of our cases and cancer in seven. The factor of occupation as an aid in diagnosis is illustrated by the following case:

Case 1 (A81308). A horseshoer came to the Clinic for advice March 2, 1913, concerning amputation for supposed sarcoma of the left femur. He had had pain for eighteen months, and a roentgenographic examination had been made and sarcoma diagnosed. Our roentgenograms showed periosteal thickening of the femur at the point where the horse's hoof usually rested, and from the clinical examination we were of the opinion it was a benign swelling due to occupational trauma. The femur was explored and no evidence of malignancy found. The patient was advised to give up his work and report later for examination. No sign of growth has appeared since then; it undoubtedly is a case of traumatic periostitis.

Trauma has been considered the cause of sarcoma of the bone; Gross gave it as a cause in 50 per cent of his cases and Escher in 39 per cent. In our series, fifty-eight patients (53.2 per cent) gave a positive history of trauma. The type of injury is significant. My experience leads me to believe that the single, hard, local injury is the type most often followed by sarcoma. Constant irritation causes traumatic periostitis; a more severe injury often causes a subperiosteal hematoma which may undergo ossification rather than absorption. In Case 2 the patient gave a history of a severe local injury several weeks before

the fracture occurred from a slight strain; this should have been suggestive of a pathologic fracture. Bissell has suggested the possibility of sarcoma following fracture; he reported it in six cases. The significant relationship between trauma and sarcoma is further borne out by the localization of sarcoma in the parts most commonly exposed to trauma. In our series, 78 per cent of the tumors were in the long bones of the knee, and 75 per cent occurred between the ages of ten and forty years, the time when injury is most likely to occur. In the first decade the tumor was around the knee, the site of common injury in children. The relationship of the type of cell in cases in which the history of trauma is positive is shown in Table 2, and the relation of age to the type of cell is shown in Tables 3 and 4.

TABLE 2
SARCOMA OF THE LONG BONES
Relation of Trauma to the Type of Cell Found—109 Cases

Type.	Patients.	Patients with trauma.
Mixed-cell sarcoma.....	52	29 (55.76 per cent)
Round-cell sarcoma.....	14	10 (71.42 per cent)
Osteosarcoma.....	18	7 (38.8 per cent)
Chondrosarcoma.....	17	7 (41.17 per cent)
Fibrosarcoma.....	8	4 (50.0 per cent)

TABLE 3
SARCOMA OF THE LONG BONES
Relation of Type of Cell to Age—109 Cases

Type.	Patients.	Average age (years).
Mixed-cell sarcoma.....	52	24.73
Round-cell sarcoma.....	14	25.85
Osteosarcoma.....	18	25.4
Chondrosarcoma.....	17	27.64
Fibrosarcoma.....	8	38.37

Case 2 (A269714). A man, aged twenty-nine years, came to the Clinic May 1, 1919, with a swelling of the lower third of the left femur. Four months before he had received a severe injury in this area, and six weeks later the femur snapped as he stepped from a curbstone. The fracture was reduced and roentgenograms showed good position. Subsequently increased swelling and the roentgenographic findings led to further consultation and the diagnosis of sarcoma, which was verified by exploration. Microscopic examination revealed round cell sarcoma. The patient refused amputation. Radium locally, roentgen ray to the chest, and Coley's toxin were advised. The patient died seven months from the date of his injury. The tumor had grown to an enormous size and had ulcerated.

TABLE 4
SARCOMA OF THE LONG BONES*
 Relation of Age to Location, 109 Cases, September, 1907 to September, 1921

Pa- tients.	Bone.		Years.						Total.
			1 to 10.	11 to 20.	21 to 30.	31 to 40.	41 to 50.	More than 50.	
49	Femur...	Right...	3	5	6	3	4	1	22
		Left....	4	5	8	7	3	..	27
27	Tibia....	Right...	1	3	3	2	..	1	10
		Left....	..	8	7	1	1	..	17
9	Fibula...	Right...	2	..	..	1	1	1	5
		Left....	..	2	1	1	..	..	4
18	Humerus	Right...	..	5	1	..	1	2	9
		Left....	..	4	2	2	..	1	9
3	Radius..	Right...	..	1	..	1	..	..	2
		Left....	..	1	..	..	..	..	1
3	Ulna....	Right...	..	..	..	1	1	..	2
		Left....	..	..	1	..	..	..	1
109			10	34	29	19	11	6	109

* Diagnosis on operation and microscopic examination.

The symptoms in the 109 cases varied with the duration and location of the tumor. The most constant symptom was mild boring pain, especially with the central or myelogenous type of tumor. When the pain is severe it is usually the result of pressure on nerves and usually occurs in the periosteal or perforating central sarcoma. Fifty-five of our patients had dull pain, twelve had severe pain, thirty-five did not state the degree of pain, and seven did not mention pain. Local swelling and varying degrees of tenderness may persist from the time of injury. The initial swelling may subside, followed in a few weeks or months by a slow or rapid growth. If the growth is in the region of a joint a secondary synovitis may result and tuberculosis may be suspected erroneously. Early evidence of disturbed circulation, as shown by enlarged veins over the tumor, is often a symptom and should be regarded as important. Such tumors occur most often in the region of the knee joint, and it is important to note that pain, if severe, is not

relieved by fixation. Joint motion is seldom impaired. Atrophy, therefore, does not occur early, and this fact, with the lack of relief by fixation, is an aid in the differentiation of tuberculosis. Further, patients continue to be up and around and are not disabled until either the tumor becomes large or pathologic fracture has occurred. Not infrequently the patient walks into the physician's office with a tumor so large that pathologic fracture is imminent. Local heat is often



FIG. 279.—Mixed-cell sarcoma of the fibula.

noticed around the tumor, and when complicated by a postoperative sinus, leukocytosis, and fever it sometimes obscures the diagnosis. In fifty-six cases in which there was a record of the blood examination the average leukocyte count was 9,929; the highest count was 29,400.

Case 3 (A289738). A girl, aged fifteen years, came for consultation September 17, 1919, stating that she had had influenza nine months before, followed by fever, and swelling in the upper left fibular area with slight pain, and loss of weight. She had been

treated for several months by medication and external applications. Five months before a curettage had been done, and three months before a piece of bone had been removed. Examination revealed a sinus over a tumor, some local heat, hemoglobin 55 per cent, and leukocytes 18,400. Roentgenograms showed destruction of the upper third of the right fibula. The tumor was explored and found to be mixed-cell sarcoma. Tourniquet was applied and amputation performed. The patient has remained well for two years (Fig. 279).

Loss of weight, pallor, and secondary anemia occur early or late, depending on the degree of malignancy, the time of metastasis, and so forth. If the patient has a cough he should be carefully examined for evidence of pulmonary metastasis, which so often is a complication.

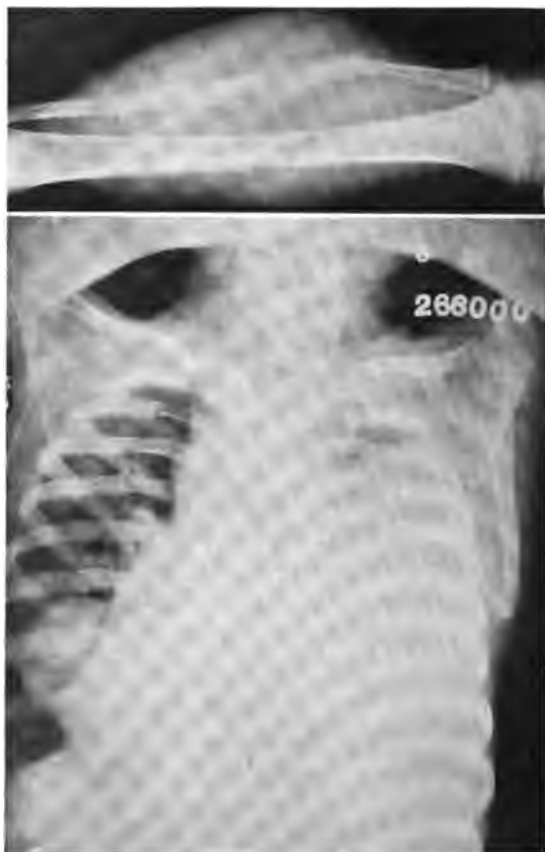
Case 4 (A266000). A boy, aged six years, was brought to the Clinic for examination March 21, 1919. He had had pain and swelling in the right leg for fourteen months. Several exploratory operations had been performed. The child had a persistent cough which had followed an attack of influenza four weeks before. A large tumor was palpable in the calf of the right leg; the circumference of the leg was 12 inches, that of the left 7 inches. The superficial veins were prominent. The temperature was 100, the pulse 118. Primary periosteal sarcoma with metastasis to the lungs was diagnosed by the roentgenogram. The patient died within a few weeks (Figs. 280 and 281).

The tumors, arising as they do from bone or periosteum, are always fixed; they are usually firm, with a gradually sloping, elevating edge rather than with the overlapping edge of an exostosis. Occasionally, on pressure, crepitus may be elicited. The differential diagnosis of tuberculosis and sarcoma in a joint or close to a joint sometimes taxes the ability of the surgeon, and aspiration or exploration may be a necessary aid. While the symptoms of sarcoma are not characteristic, any tumor with persistent, dull, boring pain should make one suspect the condition, and if the growth is rapid and the superficial veins are dilated malignancy should be suspected. Indeed, all growing tumors of the bone should be considered potentially malignant until they are proved benign.

The most characteristic symptom was localized pain. In some firm pressure disclosed tenderness, and the consistency of the tumors varied. Central lesions of the bone are not likely to be palpable until late, when the tumor passes through the bounds of the cortex and is easily outlined. Periosteal tumors usually grow more rapidly and invade the soft tissues, and thus are more easily recognized. The venous engorgement over the area of the tumor is a valuable clinical sign; it is not often noted with benign growths. Local heat is usual and in some instances marked,

although rarely accompanied by redness or pain sufficient to simulate a low grade inflammatory process, unless infection is present.

A temperature of 101 is noted in some instances, usually in the late cases. Secondary anemia and loss of weight occur rapidly in the most



FIGS. 280 and 281.—Periosteal sarcoma of the fibula with metastasis to the lungs.

malignant types of the growth, the patient usually succumbing to pulmonary metastasis. Glands are not usually involved, but they should always be examined.

Case 5 (A365027). A man, aged thirty-seven years, registered at the Clinic August 9, 1921, complaining of pain in the right knee, which he had wrenched in a jump from a wagon in 1903. There was no locking or swelling. Two operations had been performed

without appreciable results. In 1919, he had contracted influenza, and the knee had become very painful and swollen. He was unable to extend the leg. His knee had become progressively worse, and he had been obliged to use crutches. On examination, the patient was found to be in good general condition. The temperature, pulse, and blood pressure were normal. The enlarged right knee was markedly tender and painful; it was held at fixation of 160 degrees. The urine contained an occasional pus cell. The hemoglobin was 70 per cent and the leukocyte count 11,600. The Wassermann reaction on the blood was negative. Destructive arthritis of the right knee, with considerable synovial thickening, was shown in the roentgenogram. August 13, the right knee joint was opened and a sarcoma of the periosteum of the mixed-cell type was discovered. The tumor had originated on the posterior surface of the lower part of the femur and had pushed its way through to the anterior part of the joint. The thigh was amputated, and roentgen ray, radium, and Coley's toxin were given. The patient returned in two months in excellent condition and is still under treatment.

When the patient was examined in the Clinic it was believed that his condition might be tuberculous, with secondary infection following influenza. He was warned, however, of the possibility of sarcoma, and his consent was obtained for an amputation if it should be necessary. The points of interest in the history of the case are that eighteen years before the knee had been injured; it had been operated on elsewhere twice. During these years there was occasional stiffness and soreness in the knee. In 1919, following influenza, the knee became so swollen it could not be straightened. During the last six months the pain had been much more severe, and for the last two months the enlargement had been rapid. Whether the old inflammation had anything to do with the cause of the sarcoma is difficult to determine, but a few cases have been observed in the Clinic in which there was a long history of trouble of the knee joint and an apparently rapid development of sarcoma. So far as we could judge, the sarcoma in this case seemed to arise from the periosteum in the posterior part of the femur at just about the epiphyseal line. Primary sarcomas of the synovia are rare, and this case would have been regarded as a primary sarcoma of the synovia if the cross section of the specimen had not determined accurately its origin.

The roentgen ray obviously is very important in making a diagnosis and a prognosis of sarcoma of the long bones. It not only reveals the location, size, and to a certain degree the structure of the tumor, but, more important, the earliest signs of metastasis to the lungs.

Case 6 (A224826). A man, aged twenty-three years, came to the Clinic March 6, 1918, stating that he had been treated for "lockjaw" which had followed ulceration around a tooth six months before. About one month after this he noticed a swelling, without

inflammation, in the left upper tibia. Local applications and chiropractic treatments had been given. He had had some pain and had been unable to walk. The tumor had



FIG. 282.—Mixed-cell sarcoma of the tibia.

continued to enlarge. The synovitis present had been interpreted as due to bone infection; there was no history of trauma. Roentgenograms taken at the Clinic revealed



FIG. 283.—Fibrocystic disease of the upper left humerus.

increased density in the upper third of the left tibia. Examination of the chest was negative. Syphilis was suspected, but Wassermann reactions were negative. The tumor

was explored and a specimen excised. The pathologist did not find malignancy, but suggested syphilis. Intensive treatment for syphilis was given for three weeks without benefit. One month after examination the leg was amputated, and a mixed-cell, periosteal sarcoma was found. Radium, roentgen ray, and Coley's toxin were advised. The patient returned to the Clinic in nine months, complaining of slight pain in the left hip. Metastasis to the lungs and left hip was seen in the roentgenograms. The patient's weight before amputation was 134 pounds; at the time of the last examination it was 135 pounds. He died within the next year (Fig. 282).

Case 7 (A239524). A boy, aged twelve years, came for examination July, 1918, with aching, pain, and swelling in the upper third of the left humerus. The arm had been



FIG. 284.—Periosteal chondrosarcoma.

severely injured eight years before, possibly fractured. Two months before examination it had been traumatized. The arm was freely movable, and without pain or tenderness; a thickening of the upper third of the humerus was apparent. The parents and the child were greatly alarmed because cancer of the bone had been diagnosed and a Berger amputation of the shoulder advised. A diagnosis of fibrocystic disease was made in the Clinic from the clinical and roentgenographic evidence and a conservative operation advised. The thin shell of cortex was broken through and a specimen removed which verified the diagnosis; following this the wound was thoroughly curetted and closed without drainage. There was improvement in the bone as shown by the roentgenogram. The patient is alive and has good function more than three years after operation (Fig. 283).

Clinical signs of metastasis to the lungs appear long after the roentgenograms reveal the condition. The differentiation of periosteal or central (medullary) sarcomas may usually be made by the roentgenogram, although this differentiation is of doubtful value, malignancy and benignancy being the vital questions. Unfortunately we are unable to detect metastasis until the tumors are large enough to be shown by the roentgen ray (Figs. 284 and 285). Not infrequently operations are performed when metastasis has already taken place, thus giving the impression that the operation disseminates the tumor. Practically all patients ask, when exploration is advised: "But, doctor, will this spread the tumor?"

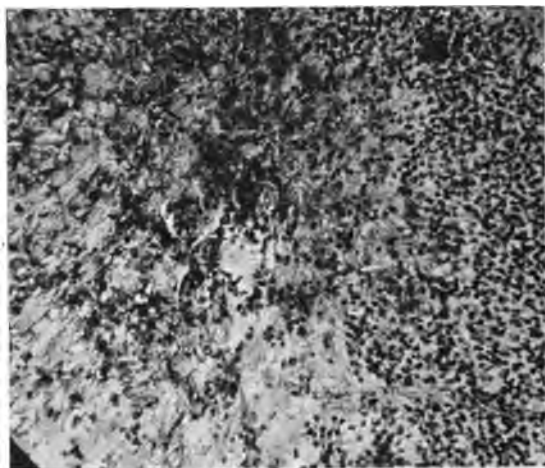


FIG. 285.—Cellular area of a chondrosarcoma ($\times 100$).

The two principal types of sarcoma of the bones are the periosteal and the central groups. The periosteal sarcoma is the most characteristic in appearance; fine lines of calcium salts in bone cast shadows of increased density which radiate outward in the manner of the sun rays, more definite at the base and fading away toward the surface. Absorption of cortical layers of bone may occur at the base of the tumor. The outlines of such tumors are usually lost in the periosteal structures so that the extent of the growth may not be judged accurately. At times this fan-like structure may be so faint as to be scarcely visible in the roentgenogram. Roentgenographic examination will not always determine the point of origin; late tumors often show cortical and medul-

lary destruction equally, and the fine radiating lines are absent. Apparently growth is too rapid to permit the formation of bone, the tumor passing rapidly into the soft tissues before this occurs.

In some cases of large osteosarcoma a slight crepitus may be palpated and the roentgenogram reveals a fine line of bone at the margin (Fig. 286). The central type of tumors more often shows undifferen-



FIG. 286.—Osteosarcoma of the right femur.

tiated body structures which cast only slight shadows and an irregular, hazy border with a tendency to invade tissues in all directions, making it impossible at times to differentiate the growth roentgenographically from carcinoma (Fig. 287). Some osteosarcomas throw a more dense shadow, appearing either as a solid bony or heavily mottled mass with irregular definite outlines. While the roentgen ray is invaluable in

showing the location and extent of lesions, and may even suggest the type of the cell structure, too much reliance must not be placed on such interpretations, since extremities may thus be needlessly sacrificed.



FIG. 287.—Round-cell sarcoma of the right humerus.

Case 8 (A168792). A woman, aged fifty-three years, was examined August, 1916. She complained of nervous indigestion, insomnia, rheumatism, and lameness of the left knee. Lameness and stiffness had been present for seven years, although there was no limitation of motion, no deformity, or tenderness. A diagnosis of sarcoma had been made elsewhere, and amputation of the hip had been advised. The urinalysis was negative; the hemoglobin was 80 per cent; the leukocytes, 5,200. The tonsils were enlarged and contained septic material. Roentgenograms showed the presence of a tumor in the lower end of the left femur. Other roentgen-ray findings were negative. August 18, the tumor was explored and found to be a chondroma. Radium was used. April 5, 1917, the tumor was curetted and the cavity filled with fat from the abdominal wall. The patient has been walking now for five years. Thus far there is no clinical or roentgenographic evidence of recurrence (Fig. 288).

The roentgenographic appearance of metastasis to the lungs varies slightly; usually there are distinct circular areas of increased density, depending on the extent and number of growths.

Treatment.—When a tumor of the bone is suspected of being malignant, roentgenograms of the chest are made routinely. The cough, with

evidences of increased intrathoracic pressure, appear too late to be of diagnostic value. Metastasis to the glands or to other structures of the body should be ruled out if possible. The extent of local growth is then determined. After all possible means have been taken to rule out metastasis and syphilis, the type of treatment must be considered. The rapidity of growth and the duration of symptoms are important. The tumor should be explored before the limb is amputated. Many radical operations have been performed and limbs needlessly sacrificed



FIG. 288.—Chondroma of the lower end of the femur.

because of failure to explore. With a tourniquet applied, exploration may be safely accomplished and the macroscopic and microscopic appearance noted.

Case 9 (A359780). A man, aged fifty-eight years, came to the Clinic May 31, 1921, complaining of pain and swelling in the upper third of the right humerus of six months' duration. He remembered that twenty years before a similar pain followed an injury and he was treated for neuritis. Just before the present attack he had twisted his shoulder. He came for consultation because sarcoma was suspected. Exploration was performed and the condition was diagnosed hemangioma. The upper half of the humerus was excised



FIG. 289.—Hemangioma of the right humerus.



FIG. 290.—Same case as in Figure 289 twenty-one days after excision and bone graft.

and a homogenous bone graft implanted. The patient recovered satisfactorily and returned to his work as a clerk (Figs. 289 and 290).

If metastasis is ruled out, the treatment may be determined to a certain extent by the duration, site, and extent of the lesion. If the treatment is nonoperative, Coley's toxin, radium, and roentgen ray is administered. If it is surgical, the growth is destroyed locally by cautery, by excision, by excision and cautery, or by amputation, followed by nonoperative measures. As I have stated, it is important to make a diagnosis early and remove the tumor in the hope of preventing local



FIG. 291.—Chondrosarcoma of the left femur.

recurrence and metastasis. Sixty-six of the 109 patients treated had amputations, nineteen had excisions and cautery, and twenty-four had local operations of various types. Early in the period of the growths local operation may appear satisfactory and patients may refuse amputation. Later the seriousness of the condition impresses them, or the tumor may be large enough to be troublesome, and patients may wish to have the operation performed in spite of the hopeless prognosis. Amputation is preferred in such cases, since many patients may remain active in their environment until metastasis causes a rapid end instead of being bedridden with a slowly destroying neoplasm (Figs. 291 and 292).

The average length of life in relation to the type of sarcoma is shown in Tables 5 and 6.

Some surgeons recommend disarticulation of the limb close to the trunk, with removal of the origin of muscle whenever possible. However, the failure to prevent metastasis, and the increased mortality seem hardly to justify such procedure until further statistical evidence of cure has been produced. Local excision, followed by cautery and radium to prevent recurrence, and roentgen ray and Coley's toxin to prevent metastasis, may give good results in selected cases. In my experience amputation and closure without drainage is the most

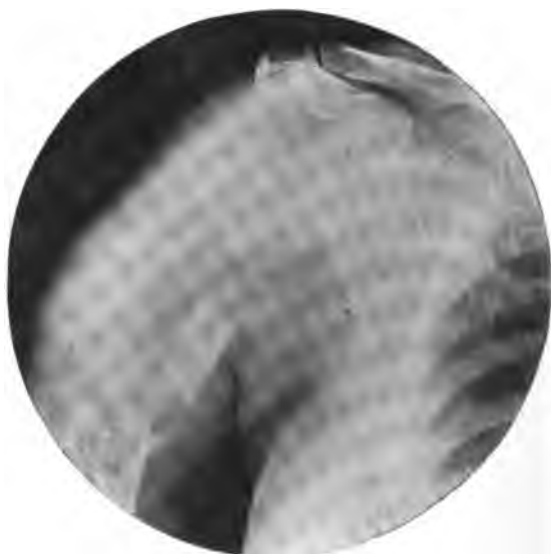


FIG. 292.—Recurring chondrosarcoma. Patient living five years after amputation.

certain means of disposing of the tumor. Local application of radium, roentgen rays over the chest, and Coley's toxin are advised following operation. It is difficult to ascribe a definite value to any one therapeutic measure when several are being used. I advise treatment by roentgen ray following operation so as to obtain diffusion of the radiation as uniform as possible in the chest and in areas of most probable metastasis whether there is or is not evidence of metastasis, since this cannot be proved until it has resulted in a growth of sufficient size and density to cast a roentgenographic shadow. During or following radium and roentgen-ray treatment Coley's serum is recommended.

TABLE 5

SARCOMA OF THE LONG BONES

Relation of Type of Cell Found to Duration of Disease in Total Number of Deaths—
Fifty-five Cases

Type.	Patients.	Average duration of disease, months.	Average length of life after operation, months.	Average total duration of disease, months.
Mixed-cell sarcoma	27	7.7	22.48	29.55
Round-cell sarcoma	9	10.8	8.6	19.5
Osteosarcoma	8	2.5	7.0	9.5
Chondrosarcoma	7	39.42	19.57	59.0
Fibrosarcoma	4	9.25	30.25	39.5

TABLE 6

SARCOMA OF THE LONG BONES: ONE HUNDRED NINE PATIENTS OPERATED ON

One Patient Died in Hospital (Mortality—0.9 Per Cent)

From September 1, 1907 to September 1, 1921

	Patients.	Per cent.
Living	47	43.11
Dead	55	50.4
Not heard from	7	6.4
Patients living		
Lived 5 years or more	14	29.78
Lived 4 to 5 years	1	
Lived 3 to 4 years	3	
Lived 2 to 3 years	3	
Lived 1 to 2 years	8	
Lived less than 1 year	18	38.29
Patients dead		
Lived 5 years or more	4	7.27
Lived 3 to 4 years	3	
Lived 2 to 3 years	6	
Lived 1 to 2 years	9	
Lived less than 1 year	31	56.36
Date of death not stated	2	
All patients		
Lived 5 years or more	18	16.51
Lived 4 to 5 years	1	
Lived 3 to 4 years	6	5.5
Lived 2 to 3 years	9	
Lived 1 to 2 years	17	15.59
Lived less than 1 year	49	44.95
Date of death not stated	2	
Not traced	7	

SUMMARY

1. Thirty-five per cent of the patients were inoperable or refused operation. In many instances undoubtedly early diagnosis would have given the patients a chance for cure.

2. Thirty-two of the fifty-five patients who died had amputations. The average duration of the disease at the time of their examination was seven and thirty-four-hundredths months, and they lived an average of fourteen and five-tenths months after operation. The average duration of life of the thirty-two patients was twenty-one and nine-tenths months. One patient who had a fibrosarcoma was examined nine months from the onset of the disease and lived thirty-six months after operation, a total of forty-five months, the longest duration of life in those who have died following amputation.

3. The most malignant sarcomas in the series of thirty-two patients were the osteosarcomas. Eight of these patients, the average duration of whose symptoms was two and one-half months before examination, lived seven months after operation, a total average of nine and one-half months.

4. Ten patients have died who had had excision and cautery. The average duration of symptoms was six and six-tenths months, the average duration of life after operation, twenty-eight and two-tenths months, and the average length of life from the time of the onset of symptoms, thirty-four and eight-tenths months. One patient with osteosarcoma, who was examined two months after the onset of the disease, died six months after a local operation. Five patients treated by excision and cautery died of pulmonary metastasis.

5. Twenty-one (31.8 per cent) of the sixty-six patients in the series who had amputations are reported to have died of metastasis to the lungs. The average length of life of these patients was twenty-one and nine-tenths months.

6. The value of microscopic proof of malignancy of tumors of the long bones is obvious, inasmuch as the fate of an extremity may depend on such proof. If any doubt exists with regard to the character of the tumor, section from various portions should be examined.

7. A diagnosis should be made only after thorough clinical, physical, and roentgenographic examinations have been made, and even then cannot always be determined until an exploratory operation and microscopic examination rules out giant-cell tumor, chondroma, fibrocystic

or cystic disease, syphilis, and osteomyelitis. The principal points to be decided before operating are malignancy, metastasis, and the extent of bone involved. With early diagnosis, with eradication of the tumor, with care to exclude patients with metastasis, and with the use of radium, roentgen ray, and Coley's toxin prolongation of life may be looked for following operation.

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BRAIN, SPINAL CORD, AND NERVES

THE STUDY OF VESTIBULAR NERVE FUNCTION IN MYXEDEMA*

ROY A. BARLOW

The study of the phenomenon of lowered irritability was suggested by the occasional finding of nerve deafness in certain myxedematous patients. As we know, myxedema, or hypothyroidism, is a condition arising from disfunction of the thyroid gland and manifesting itself by change in weight, cardiac disturbances, dry skin, and other visceral upsets, associated with a certain slowness in response to external stimuli.

From time to time additional data have been added to our knowledge of the interesting condition of myxedema. In recent years light has been thrown on the clinical picture of the condition by the work of Plummer, and Boothby and Sandiford, along the lines of the basal metabolic rate. This work, in conjunction with the isolation of the active principles of the thyroid gland by Kendall, has been of inestimable value in the manipulation of such cases. The literature on the subject has been well combed and brought to date by Lissner, who discusses at length the various changes in the special senses in cretins and in myxedematous patients. St. Lager has reported 5,000 cretins in Switzerland and 4,000 deaf mutes; 80 per cent of the latter were cretins. Scholz found that 29 per cent of cretins were deaf mutes and that 32 per cent of the others were hard of hearing. Hammerschlag, who was one of the first carefully to investigate the condition, found peripheral ear changes and disturbances in the bone conduction. Various theories and hypotheses have been advanced with regard to the changes taking place, such as ossification of the stapes, impaired development of the epithelial cells in the ductus cochlearis, and so forth. In cases in which the thyroid gland has developed a disfunction after puberty, marked disturbances of hearing are found which can readily be distinguished from the endemic variety by the rapid and spectacular improvement following thyroid therapy.

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Lisser calls attention to the fact that Wagner supposed the impairment in hearing was due to myxedematous swelling of the mucous membrane of the middle ear, but Denker found that in thyroidectomized dogs that had become entirely deaf after operation, there were no histologic changes of a myxedematous character, and stated that the question remained unsettled. It was this statement that prompted me to investigate, clinically, the eighth nerve tracts by equilibration tests.

The literature on the subject of myxedema, which is most voluminous, constantly directs attention to the fact that such patients complain of deafness and tinnitus, but nowhere in the available literature have I been able to find a single reference based on the function of the eighth nerve tracts as demonstrated by the Bárány tests. While the results of my investigation may not be of paramount value in themselves, they are nevertheless an additional bit of data to the sum total of recorded findings.

Fifteen cases of myxedema were studied; these had been definitely diagnosed as such by the clinical findings in conjunction with the various laboratory tests, most noteworthy of which is the determination of the basal metabolic rate. I shall not dwell on the various changes, such as dry skin, lack of perspiration, and so forth, nor quote profuse statistical material which in itself is more or less confusing, but shall make a preliminary report on the cases studied thus far. The equilibration test was made at about the same time as the basal metabolic rate was taken. Some of the patients were placed on thyroid therapy and have reported their improvement by proxy. Except in one or two instances they have not as yet been tested to note the improvement, if any, in the eighth nerve tracts.

SUMMARY OF CASES

Case 1 (A200923). Mrs. R. O. L., aged forty-nine years, came for examination July 14, 1917, complaining of indefinite gastric symptoms and increased weight. The general examination was negative. February 28, 1918, the basal metabolic rate was taken and found to be -17 per cent.

The hearing test showed a slight nerve involvement such as is seen with edema of the internal ear. The equilibration test showed a definite reduction in irritability, especially on the left side. The reduction was most marked in the reaction time.

Case 2 (A235663). Miss T. R., aged eighteen years, was examined June 20, 1918. She had metrorrhagia, and appeared anemic. Her hemoglobin was 65 per cent and her basal metabolic rate, taken June 22, was -32 per cent.

The hearing tests were normal. Equilibration tests showed a slight spontaneous nystagmus and delayed induced nystagmus; the amplitude also was reduced. The

pointing response was of doubtful significance. This case shows mainly a reduction in time and amplitude of nystagmus.

Case 3 (A236779). Mrs. J. H. P., aged sixty-two years, came for consultation July 5, 1918. In the course of examination it was found that she had a basal metabolic rate of -32 per cent.

The equilibration tests showed that the stimuli went through, but with reduction in time in nystagmus for horizontal tracts and reduction in amplitude for vertical tracts. Hearing tests showed an eighth nerve reduction, hearing nothing in Schwabach test. She was given thyroxin in 0.25 mg. doses three times a day and August 1, 1918, her basal metabolic rate was $+1$ per cent. Symptomatically she was greatly improved. A Bárány test was attempted. The hearing had improved. In an attempt to test the tracts with cold water she became violently nauseated and the test could not be continued. She had a decided sensation of falling.

This is the only case in the series in which an opportunity was afforded to check up after treatment. The findings indicate that it may be possible in later studies to demonstrate improvement in the results of the Bárány tests.

Case 4 (A262235). Mrs. W. A. E., aged forty-nine years, was examined February 28, 1919. She stated that she had noticed an increase in weight, pallor and puffiness, and a change in voice tone. Her skin was dry and her mentality somewhat retarded. General examination was negative, except that the hemoglobin was 10 per cent, and the basal metabolic rate was -22 per cent.

The hearing test showed some reduction in tone appreciation. The equilibration test showed no spontaneous nystagmus and a reduction in amplitude of induced nystagmus, although time reaction was not disturbed. The pointing reaction was not brought out, although there was a slight spontaneous fault with the left.

Case 5 (A262555). Mr. F. M., aged thirty-nine years, a farmer, came for examination March 4, 1919, complaining of progressive muscular weakness of four years' duration. His skin was yellowish white. His muscular movements had become markedly slower and he had difficulty in keeping warm. His basal metabolic rate was -40 per cent and his weight was 142.5 pounds.

The equilibration examination showed that in addition to a lowered bone conduction there was no spontaneous nystagmus. The nystagmus induced with caloric irrigation showed slight delay and diminished amplitude in the rotatory nystagmus. There was almost no vertigo. The pointing was not brought out with the head erect in the right horizontal canal, but was well elicited with the head thrown back. The left did not respond on the right when the left canal was stimulated, but was present with the left hand.

Case 6 (A270161). Mrs. W. S., aged forty-five years, was examined July 7, 1920. She had had a thyroidectomy and her symptoms pointed to insufficient thyroid function. Her basal metabolic rate was -28 per cent.

The equilibration test was negative. The hearing test was normal. The nystagmus time was prompt and the amplitude well marked. There was no past pointing fault, save a failure to respond on stimulation of the left ear, and past pointing with the right hand with the head erect. Other than this discrepancy, it might be said that this patient showed very slight, if any, disturbance as demonstrated by the Bárány test.

Case 7 (A281940). Mrs. H. M. A., aged fifty-one years, came for examination August 1, 1919 complaining of general lethargy and decrease in weight. She noticed that she had difficulty in remembering, that mentally she did not grasp things. Her basal metabolic rate was -39 per cent.

Hearing tests were normal, but equilibration tests showed a slight spontaneous

nystagmus on looking to right or left and a delayed time in after-nystagmus, with reduction in vertigo. The induced nystagmus was missing in the verticals even after three minutes' irrigation, although the pointing responses were elicited. The horizontal canals gave fair response with the head thrown back. There was no nausea with stimulation. The cerebelli were in normal response, but the reduction was largely in the midstem.

Case 8 (A284646). Miss L. W., aged fourteen years, came for examination August 2, 1919, complaining of loss of appetite and weight, and considerable weakness. Her parents had noticed that she was slow of speech and somewhat mentally dull. The examination of the heart, lungs, and kidneys was negative. Her hemoglobin was 74 per cent and her basal metabolic rate was -36 per cent.

The hearing tests were normal. The equilibration tests showed a spontaneous nystagmus horizontal. On irrigation the nystagmus from the vertical tracts was found to be delayed; the after-nystagmus in the horizontal tracts was prompt on the right, but not induced on the left. There was also a decrease in the past pointing response from the left with the head thrown back. Otherwise the past pointing was fairly prompt.

Case 10 (A307493). Miss G. H., aged twenty-six years, was examined February 27, 1920. She presented rather an indefinite clinical picture, with gradual onset of abdominal distress and some increased nervous instability. Her basal metabolic rate was -22 per cent; her weight was 119.25 pounds.

The equilibration tests showed practically normal hearing. The patient had a slight spontaneous nystagmus, but no pointing fault. Under caloric stimulation she showed a delay in responses, but no nausea. The pointing reaction was not materially interfered with except the horizontal canal, and it should be noted that the degree of amplitude in the nystagmus induced was less than with the head thrown back. There was no tendency to falling. Irritability was reduced.

Case 12 (A324843). Mrs. M. F. T., aged sixty-seven years, came for examination July 16, 1920, complaining of abdominal distention, constipation, shortness of breath, puffiness under the eyes, and swelling of extremities. The routine examination revealed a basal metabolic rate of -17 per cent July 23, and -26 per cent July 28.

The hearing test was normal and equilibration tests showed no spontaneous disturbance either of nystagmus or pointing. The nystagmus on stimulation was not delayed. There was only slight nausea. The past pointing was elicited well, except on stimulation of the left ear, with the head back, when the left side did not respond, although the right was quite pronounced.

Case 13 (A313335). Mrs. M. L., aged fifty-seven years, came for examination April 22, 1920. She had a malignant tumor of the thyroid. Her basal metabolic rate was -25 per cent.

The equilibration test showed slight deafness; no spontaneous nystagmus or pointing fault. On caloric stimulation she was found to have a slight delay in nystagmus time and a slight reduction in past pointing. She was weak and it was doubtful how much the hypothyroidism influenced the tests, or whether the delayed responses might be explained by the patient's weakened condition.

Case 14 (A331963). Mrs. J. N., aged fifty-three years, was examined August 30, 1920. The routine tests were made. The basal metabolic rate was -26 per cent.

The hearing test showed only a slight lowering of bone conduction. Equilibration test showed a slight spontaneous nystagmus on looking to the right. On caloric stimulation she was found to have prompt responses of good amplitude. There was good response in the past pointing. Altogether, this case showed very slight changes of indeterminate significance.

TABULATION OF THE CASE HISTORIES

CASE 1 (A200923)

Spontaneous responses.								
Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent.....	Whisper	Whisper	Touch	Touch	←	→	0	0
Weber's test.....	+	+						
Rinne's test.....	+	+						
Schwabach's test...	-2	-2						
C-1.....	-5	-5						
C-4.....	-6	-6						

Caloric test—68 F.

Remarks:								
Irritability definitely reduced throughout.	1	3	↶1'40"	↷1'40"				
	1	2	→	←				

CASE 2 (A235663)

Spontaneous responses.								
Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent.....	Whisper	Whisper	Touch	Touch	←	→	0	0
Weber's test.....	+	+						
Rinne's test.....	+	+						
Schwabach's test...	Normal	Normal						
C-1.....	Normal	Normal						
C-4.....	Normal	Normal						

Caloric test—68 F.

Remarks:								
Nystagmus very slight, slowly induced; irritability markedly reduced.	Touch	Touch	↶1'10"	↷1'				
	1	2						
	1	1						
	Touch	Touch	→	←				

CASE 3 (A236779)

Spontaneous responses.

Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent.....	Loud whisper	Loud whisper	Touch	Touch	0	0	0	0
Weber's test.....	+	+						
Rinne's test.....	+	+						
Schwabach's test...	-7	-6						
C-1.....	-20	-14						
C-4.....	-15	-10						

Caloric test—68 F.

Remarks:								
Responses retarded.			2	2	↪2'10"	↩1'15"		
			2	2				
			2	Touch	→	←		
			2					
			Touch					

CASE 4 (A262235)

Spontaneous responses.

Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent.....	Whisper	Whisper	Touch	Touch	0	0	0	0
Weber's test.....	+	+						
Rinne's test.....	+	+						
Schwabach's test...	Normal	Normal						
C-1.....	-10	-6						
C-4.....	-8	-6						

Caloric test—68 F.

Remarks:								
Time normal; amplitude and responses markedly reduced.			Touch 1	Touch 1	↪1'35"	↩1'40"		

CASE 5 (A262555)

Spontaneous responses.								
Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent.....	Whisper	Whisper	Touch	Touch	0	0	0	0
Weber's test.....	+	+						
Rinne's test.....	+	+						
Schwabach's test...	-5	-5						
C-1.....	Normal	Normal						
C-4.....	Normal	Normal						

Caloric test—68 F.

Remarks:

Responses delayed, amplitude small.

Touch	Touch	↷1'5"	↶1'20"		
Touch	Touch				
4	6	→	←		
	6				
	8				

CASE 6 (A270161)

Spontaneous responses.								
Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent.....	Whisper	Whisper	Touch	Touch	0	0	0	0
Weber's test.....	+	+						
Rinne's test.....	+	+						
Schwabach's test...	Normal	Normal						
C-1.....	Normal	Normal						
C-4.....	Normal	Normal						

Caloric test—68 F.

Remarks:

Responses normal, slightly reduced.

4	4	↷1'	↶1'30"		
6	8				
2	4	→	←		
4					
Touch					

CASE 7 (A281940)

Spontaneous responses.								
Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent.....	Whisper	Whisper	Touch	Touch	←	→	0	0
Weber's test.....	+	+						
Rinne's test.....	+	+						
Schwabach's test...	-4	-3						
C-1.....	Normal	Normal						
C-4.....	Normal	Normal						

Caloric test—68 F.

Remarks:								
Rotatory nystagmus not induced.			3	2	0	3'	0	3'
Rotatory nystagmus not induced.			14	4				
			2	3				
				3	→	←		
				Touch				

CASE 8 (A284646)

Spontaneous responses.								
Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent.....	Whisper	Whisper	Touch	Touch	→	←	0	0
Weber's test.....	+	+						
Rinne's test.....	+	+						
Schwabach's test...	Normal	Normal						
C-1.....	Normal	Normal						
C-4.....	Normal	Normal						

Caloric test—68 F.

Remarks:								
Irritability reduced throughout; no localization.			4	2	↷1'4"	↶1'30"		
			4	1				
			5	Touch	→	0		
			6					
			1					

CASE 9 (A285377)

Spontaneous responses.								
Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent.....	Whisper	Whisper	Touch	Touch	←	→	0	0
Weber's test.....	+	+						
Rinne's test.....	+	+						
Schwabach's test...	Normal	Normal						
C-1.....	Normal	Normal						
C-4.....	Normal	Normal						

Caloric test—68 F.

Remarks:								
No rotatory nystagmus after three minutes, reduced horizontal; responses reduced.	1	3	0	3'	0	3'		
	1	1						
	2	Touch	→		←			
	1	Touch						

CASE 10 (A307493)

Spontaneous responses.								
Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent.....	Whisper	Whisper	Touch	Touch	←	→	0	0
Weber's test.....	+	+						
Rinne's test.....	+	+						
Schwabach's test...	Normal	Normal						
C-1.....	Normal	Normal						
C-4.....	Normal	Normal						

Caloric test—68 F.

Remarks:								
Responses delayed, irritability reduced; no nausea.	2	3	↖1'26"	↖1'32"				
	6	4						
	2	3	→	←				
	4	4						

CASE 11 (A308604)

Spontaneous responses.							
Hearing.			Pointing.		Nystagmus.		
	Right.	Left.	Right.	Left.	Right.	Left.	Up. Down
Noise apparent.....	Whisper	Whisper	Touch	Touch	0	0	0 0
Weber's test.....	Normal	Normal					
Rinne's test.....	+	+					
Schwabach's test...	-2	-2					
C-1.....	-2	-2					
C-4.....	-4	-7					

Caloric test—68 F.

Remarks:

Responses delayed.

Responses delayed.

1	3	↷1'23"	↶1'40"
3	5		
1	4	→	←
3	5		

CASE 12 (A324843)

Spontaneous responses.							
Hearing.			Pointing.		Nystagmus.		
	Right.	Left.	Right.	Left.	Right.	Left.	Up. Down.
Noise apparent.....	Whisper	Whisper	Touch	Touch	0	0	0 0
Weber's test.....	+	+					
Rinne's test.....	+	+					
Schwabach's test...	Normal	Normal					
C-1.....	Normal	Normal					
C-4.....	Normal	Normal					

Caloric test—68 F.

Remarks:

Time delayed; amplitude small.

10	8	↷1'	↶1'15"
10	6		
10	6	→	←
10	Touch		

CASE 13 (A813335)

Spontaneous responses.								
Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent.....	Whisper	Whisper	Touch	Touch	0	0	0	0
Weber's test.....		+						
Rinne's test.....	+	-						
Schwabach's test...	Normal	Normal						
C-1.....	Normal	-12						
C-4.....	Normal	-2						

Caloric test—68 F.

Remarks:								
Responses slightly delayed.		2	2	↷1'10"	↶0'50"			
Responses delayed.		3	3	→	←			
			2					
			3					

CASE 14 (A331963)

Spontaneous responses.								
Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent.....	Whisper	Whisper	Touch	Touch	0	0	0	0
Weber's test.....	Normal	Normal						
Rinne's test.....	+	+						
Schwabach's test...	-6	-6						
C-1.....	Normal	Normal						
C-4.....	Normal	Normal						

Caloric test—68 F.

Remarks:								
Responses fine in character, prompt.		6	4	↷0'45"	↶0'35"			
Responses prompt; slight nausea.		4	4	→	←			
		5	4					
		4	4					

CASE 15 (A359522)

Spontaneous responses.								
Hearing.			Pointing.		Nystagmus.			
	Right.	Left.	Right.	Left.	Right.	Left.	Up.	Down.
Noise apparent.....	Whisper	Whisper	Touch	Touch	←	0	0	0
Weber's test.....	+	+						
Rinne's test.....	+	+						
Schwabach's test...	-2	-2						
C-1.....	-8	-10						
C-4.....	-3	-2						
Caloric test—68 F.								
Remarks:								
Responses somewhat slow.			Touch	Touch	0 3'	← 1'45"		
			9	2	→	←		
			2	2				
				2				
				3				

On the Bárány sheets it may be noted that retardation in response was demonstrable in 73 per cent of the cases. Cases 1, 2, 7, 8, 9, 10, and 15 show spontaneous nystagmus. Lowered bone conduction* was noted in Cases 5, 7, and 14 only. "Lowered bone conduction" indicates that bone conduction was demonstrated to be lowered in an otherwise normal hearing test, or lowered out of proportion to the rest of the hearing test. There was no spontaneous pointing fault noted.

The caloric test consisted of irrigating the ear with water at 68 F. The nystagmus produced, if any, was recorded; the past pointing test was then made, the head was thrown back, and the nystagmus, if any, was noted; the past pointing test was again made. The most prominent finding was that of a delayed response in time or a reduction in amplitude of nystagmus or past pointing, or a combination of all. The degree of retardation was variable, as, for instance, in Case 15, in which nystagmus was absent when the right ear was irrigated and past pointing fault was not noted with the head erect, as compared with Case 6 in which the nystagmus was prompt on the right and responses fairly normal. Case 7 gave no response to stimulation with the head in an erect position with nystagmus, but, nevertheless, the stimulus penetrated sufficiently to produce a past pointing fault, with

* The author published an article on lowered bone conduction test in 1918.

the exception of the left hand and on stimulation of the right ear. In this case, however, with the head thrown back a prompt response was obtained in the nature of a horizontal nystagmus and a well-marked past pointing response. In Cases 1, 2, 3, 8, 10, 11, and 13 there was a generalized retardation or reduction in response to caloric stimulation. In Cases 2, 4, 5, 12, and 14 a reduction in amplitude of the nystagmus and after-nystagmus was found. In Case 3 the responses were retarded, the past pointing test with the right hand and on stimulation of the left ear was not elicited, and the past pointing tests throughout were somewhat reduced. The patient was placed on thyroid therapy and was found within four weeks to have a basal metabolic rate of +1 per cent. She was symptomatically improved, but an attempt to test with the equilibration method was unsuccessful because she was made extremely nauseated and dizzy by the stimulation. In only this one case in the series was it possible to note the effect of the thyroid therapy, but the difference was sufficient to warrant the suggestion that, possibly, thyroid therapy would be beneficial in all of the cases.

In analyzing these cases it was found that the degree of disturbance in the basal metabolic rate in no way indicated the changes that were noted by the Bárány test. The changes are not constant, they are not localized to any one region, and are not of the same degree throughout. I believe that the tests demonstrate the fact that myxedema is a condition in which, besides the other changes, there are disturbances of response to stimuli in the eighth nerve tracts which coincide with response to stimuli in other nerve tracts. The exact nature of the pathologic condition causing this disturbance is a matter of conjecture. It may possibly be due to edema of the nerve, to the associated anemia, or it may be a combination of these associated with what may be called a psychical disturbance or high grade weakness in the higher centers.

CONCLUSIONS

1. In cases of myxedema there is a definite clinical vestibular picture which can be demonstrated by the equilibration tests and is in the nature of a delayed response to stimuli.
2. There is no relationship between the basal metabolic rate and the degree of this retardation.
3. The one case noted suggests the possibility that this clinical picture may be improved by thyroid therapy.

4. These cases are sufficiently interesting to warrant further investigation.

5. The foregoing data may be of very little value in itself, but adds materially to the sum total of clinical information.

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BILATERAL ABDUCTOR LARYNGEAL PARESIS*

GORDON B. NEW

Since the work of Semon, in 1881, on the abductor muscles of the larynx we have known of their proclivity to become affected first in lesions of the recurrent laryngeal nerve or in central lesions. I have not, however, been able to find in the literature a case in which the abductor muscles have given out under direct observation after repeated phonation, and have returned after rest to their normal function.

Hooper and, later, Donaldson, in experimental work on dogs, stimulated the recurrent laryngeal nerve with an electric current and observed the effect on the cords. Hooper obtained abduction of the cords, but Donaldson found that this was due to a weak current; when the current was increased the abduction gradually passed into adduction, and after a strong and constant stimulation the abductor muscles became worn out and ceased to respond to stimuli. Semon and Horsley killed a group of dogs by an overdose of anesthetic, by puncture of the heart, or by bleeding. The larynx was immediately excised and the muscles of the larynx rapidly laid bare by dissecting off the mucous membrane. The muscles were then stimulated by an ordinary platinum electrode, the current being obtained from a Dubois-Reynold's sledge induction coil and supplied by a Daniell cell. The results proved with remarkable constancy that the abductor muscles lose their excitability long before the adductor muscles.

Russell, in experiments on the recurrent laryngeal nerves in dogs, demonstrated that the abductor and adductor fibers are in two distinct bundles which can be isolated, and that the abductor fibers are situated on the inside of the nerve. Stimulation of these bundles separately produced, respectively, abduction or adduction, and cutting one bundle produced muscle degeneration in the muscle or muscles which it supplied. Russell traced, anatomically, the nerve fibers of each bundle to the muscle or muscles which they supplied.

A case is reported here of chronic anterior poliomyelitis with bulbar involvement, in which the abductors of the cords ceased to function

* Reprinted from the *Laryngoscope*, 1921, xxxi, 630-632.

entirely on one side, and functioned only partially on the other when the patient phonated repeatedly, while the larynx was observed with the laryngeal mirror.

Case A348390. Mr. J. B. McG., aged sixty-four years, came to the Clinic February 8, 1921. He had been quite well until four years before, when he noticed a beginning left foot drop. This gradually increased and the muscles of the left leg grew smaller. For the last few months he had noticed that his right leg was growing weaker and smaller and that his back was growing weak; he had to use his hands to get on his feet from a sitting position. He had noticed difficulty in speaking for the last few months, and the character of his voice had changed in the last ten days.

At the time of his examination he walked with a limp and a foot drop, and used a cane. His normal weight which had been 200 pounds was 185 pounds. His systolic blood pressure was 160; his diastolic 90. He had some arteriosclerosis. His vision was 6/10 and 6/5; the fundus was negative. Blood and spinal fluid Wassermann reactions were negative. The neurologic examination revealed a marked atrophy of the lower extremities, with corresponding loss of strength and fibrillary twitchings. In the upper extremities the corresponding loss of strength and fibrillary twitchings were moderate. The deep reflexes were diminished in both upper and lower extremities; the left tendo achillis reflex was absent. There were no plantar extensor phenomena or indication of syphilitic involvement. When the patient's larynx was first examined both cords moved quite normally. On repeated phonation, the abductors on the right side completely gave out, and the right cord was in the position of complete abductor paralysis. On the left side the abductor gave out about one-half, and the abduction was graded 2 on a scale of 1 to 4. After the patient had rested for from five to ten minutes the cords again moved quite normally. This phenomenon was repeated a number of times and was observed by several physicians, so that the change in the movement of the cords was unquestionable.

A partial or complete abductor paralysis due to involvement of the recurrent laryngeal nerve or to central lesions is often seen, but this is the first time that I have observed a case in which the use of the voice for a fraction of a minute tired out the abductors so that they could not function until rested. The condition of the nerve supply was responsible.

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TUMORS INVOLVING THE GASSERIAN GANGLION*

WALTER D. SHELDEN

The relative infrequency of involvement of the gasserian ganglion by tumor is my justification for presenting this subject for your consideration.

In 1900, Dercum, Keen, and Spiller reported the first case in the English literature of tumor involving the gasserian ganglion and the second to be treated by surgical measures. In 1918, Frazier reported forty cases from the literature and three of his own. Thirteen of these, including his three cases, were treated surgically.

The literature on the subject has been so thoroughly reviewed by Spiller, Hellsten, Frazier, and others^{1, 6, 8} that to repeat it seems unnecessary. I shall, therefore, confine my discussion largely to the data concerning the four cases here reported.

REPORT OF CASES

Case 1 (A125267). Mr. J. F., aged twenty-six years, was examined February 25, 1915. He had had tuberculosis of the right knee at the age of twelve, the recovery resulting in ankylosis; an abscess of the rectum at sixteen; typhoid at seventeen; and an acute otitis media of the right ear at twenty-two. Eighteen months before he began to have pain in the right cheek and in front of the right ear with radiation toward the chin associated with burning within the cheek and on the right side of the tongue. The pain was almost constant with occasional severe exacerbations; it was intensified by lying on the left side, by pressure in the right auditory meatus, or by blowing the nose. For five months he has not been able to open his mouth as wide as usual and the jaw deviated to the right. During the last month he noticed that the right pupil had become smaller than the left; that the right cheek, chin, and the right side of the tongue were numb, that fluids escaped unnoticed from the right side of the mouth, that taste was impaired on the right side of the tongue, and that his voice had developed a nasal quality. Following a cold about six weeks before the glands below the left jaw had enlarged, and after ten days incision and drainage were required.

The patient was 20 pounds underweight, but his color was good. The general examination was negative, except for enlarged glands under both jaws, the left the larger. Glands taken from both sides were found to be tuberculous on microscopic examination.

* Presented before the Section on Nervous and Mental Diseases at the Seventy-second Annual Session of the American Medical Association, Boston, June, 1921. Reprinted from the Journal of the American Medical Association, 1921, lxxvii, 700-705.

The Wassermann test of the blood was negative. The right pupil was smaller, the vision in the right 20/30, in the left 20/20; the light and convergence reactions were normal, the fundi were negative, the right corneal reflex was practically lost, the ocular movements were normal, but there was a slight ptosis of the right lid. The sensation disturbance of the right fifth nerve was unusual. Touch was lost over the chin and moderately impaired over the cheek, while over the forehead it was normal and equal with the left. Recognition of head and point was lost over the chin and the cheek, and much impaired over the forehead. Temperature was most impaired over the chin, but was not

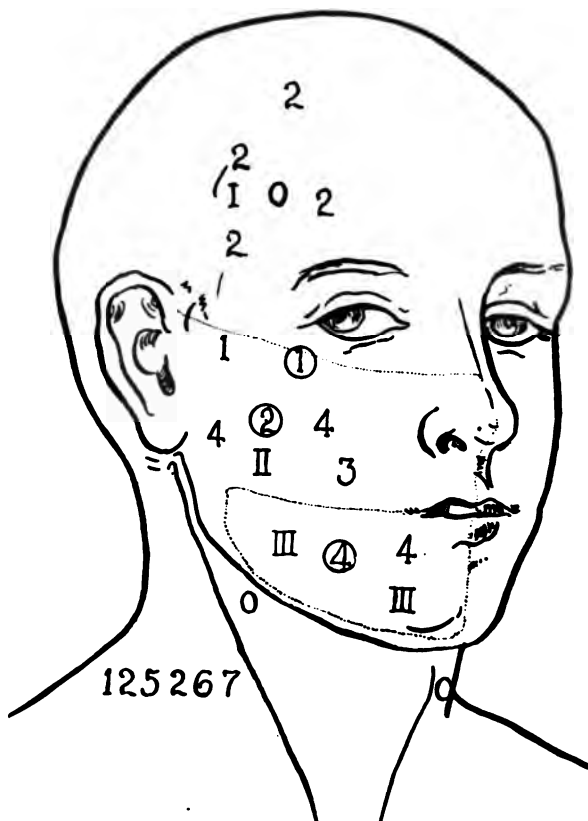


FIG. 293 (Case 1).—Anesthesia chart: Tactile disturbance, 0 to 4 in circle; pain disturbance, 0 to 4; temperature disturbance, 0 to IV.

abolished; it was impaired, but less so than pain over the cheek and forehead. The quite definite dissociation of sensation remained constant throughout the period of observation. Heat and cold were not specified separately. The masseter and temporal of the right side were weak and the jaw deviated to the right on opening. The soft palate was weak on the right side. The remainder of the central nervous system was negative. Hearing was normal in the left ear. The right drum was greatly retracted and contained a small perforation causing moderate impairment of hearing.

The patient was examined several times during the period from February to July.

this interval being employed for a therapeutic test with mercury rubs and potassium iodid. A septum operation was performed for a high deflection with a septal spur. This gave a good functional result, but the pain was not modified. The right antrum was irrigated because of defective transillumination, with negative results. In May, double vision was first noticed, due to weakness of the right external rectus. This increased gradually and remained constant. In June, ptosis seemed more pronounced, but transient. By July, the motor fifth was completely paralyzed, as was also the right side of the soft palate. At this time a gland was removed from the left side of the neck and on microscopic examination proved to be tuberculous.

Notwithstanding the presence of glandular tuberculosis, we believed we were warranted in exploring the gasserian ganglion region. A spherical tumor about 1 cm. in diameter coming directly from the tissue around the ganglion was removed (Beckman). The microscopic diagnosis of the tumor was endothelioma (Figs. 293 and 294). Two weeks later a gland removed from the right side of the neck was also found to be tuberculous.

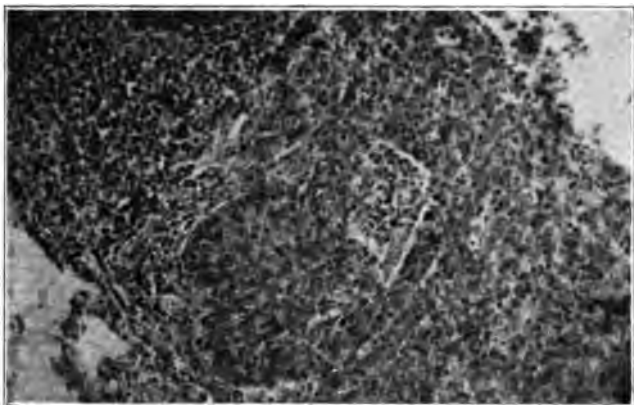


FIG. 294 (Case 1).—Endothelioma (this tumor is indistinguishable from squamous-cell epithelioma of a high degree of malignancy) ($\times 100$).

For a month following the operation there was no pain, after which it gradually returned in the same area. In September and October alcohol injections were given in an attempt to relieve the pain, but with no definite result. Further observation was not made, but information was received that the patient's symptoms gradually intensified until his death in July, 1916.

Case 2 (A232362). Mrs. D., aged forty-five years, examined May 25, 1918, had had good health except for attacks of diphtheria four years and two years before. About six months before the onset of her present symptoms she received a severe blow on the forehead, which did not cause unconsciousness, nor was there any evidence of fracture. She had had tinnitus, especially in the left ear, for two or three years. One and one-half years before coming to the Clinic she began to have severe steady pain in the left cheek, which had been practically constant since onset. All the teeth had been removed, and the left antrum had been opened five months before, without relieving the pain. The last two months, a hoarseness and some difficulty in swallowing had developed. For a considerable period, she had had epileptiform attacks at intervals of two

weeks. Several alcohol injections had been made without relief, although the numbness in the face was considerably increased by them. The patient was quite weak, emaciated, and suffering from severe pain.

There was complete paralysis of the left external rectus and also slight ptosis. The left pupil was slightly smaller than the right; the pupillary reaction to light was markedly reduced; the reaction to convergence was normal. The fundi were normal. There was slight nystagmus on looking to the right. The left masseter and temporal muscles were greatly weakened and the jaw deviated to the left. Tactile sensibility was lost over the left chin and the angle of the mouth, and it was pronouncedly impaired over the left

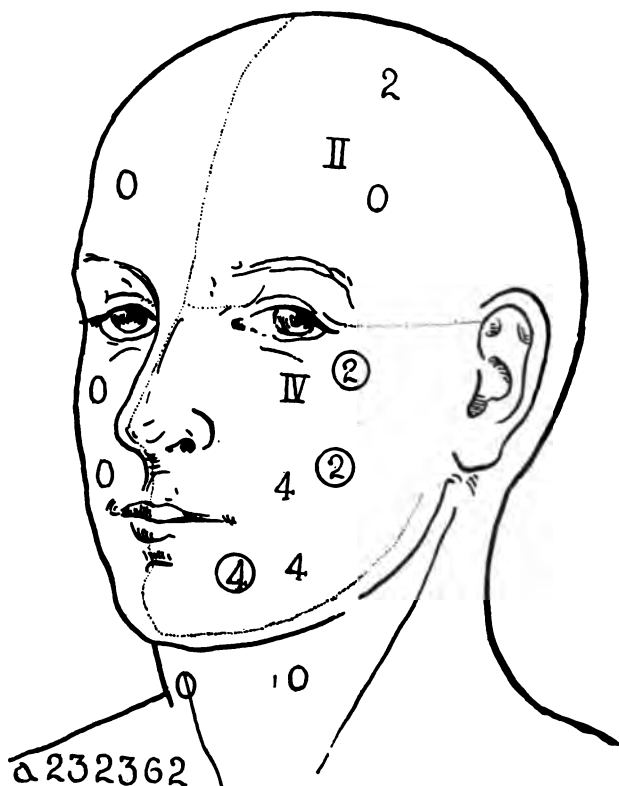


FIG. 295 (Case 2).—Anesthesia chart.

cheek, the degree gradually lessening toward the forehead, where it was normal. Pain and temperature sensibility were lost over both the chin and cheek and were moderately impaired over the forehead. The left auditory meatus was anesthetic to pin-prick. The left side of the face seemed a trifle flat, but the power seemed normal. The watch-tick was not heard in either ear and tests with the forks indicated a marked nerve deafness in both ears, especially the left. The soft palate was pulled toward the right and fluids were often deflected through the nose on swallowing. The left vocal cords were paralyzed. The left sternomastoid was weak. The left half of the tongue was markedly atrophic with fibrillary twitchings near the tip. The reflexes of the arms were normal; the knee

and Achilles on the left were somewhat more active than on the right and there was a Babinski response from each foot. The abdominal reflexes were absent. The sensation with the exception of that of the face, the coordination, the station, and the sphincter control were normal.

June 15, an attempt was made to relieve the severe pain by section of the posterior root of the fifth nerve. Through the usual approach the ganglion with a portion of the tumor was removed en masse and the posterior root cut. A partial paralysis of the left seventh nerve appeared after the operation. Only temporary relief from the pain was obtained. The pathologist diagnosed endothelioma (Figs. 295 and 296). In December, 1918, a report from her physician stated that symptoms continued with gradually progressive emaciation until death.

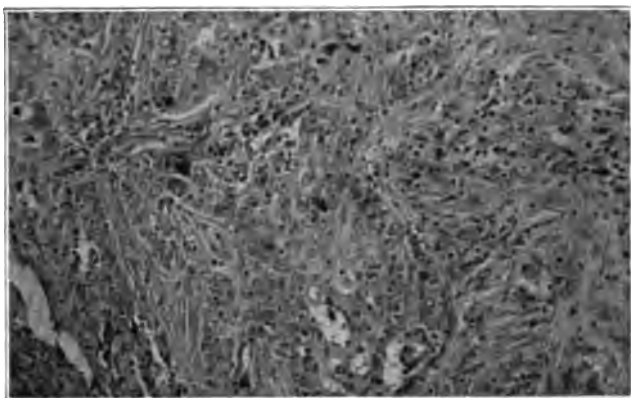


FIG. 296 (Case 2).—Endothelioma (this tumor is indistinguishable from squamous-cell epithelioma of a high degree of malignancy) ($\times 100$).

Case 3 (A231496). Mrs. Z., aged forty-seven years, was examined May 15, 1918. She had always been in good health, was well nourished, and had a good color. Eleven months before she began to have severe pain on the left side of her head, this had been practically constant since. Six months before, a convergent strabismus appeared in the left eye. All the teeth on the left side had been removed, and a nasal operation had been performed five months before, but without relief.

The general examination was negative. The blood and spinal fluid were negative. Vision in the right eye was 6/6, in the left 6/15. The pupils were equal, and pupillary reaction was normal, the fundi and fields were negative. The left external rectus was paralyzed. The upward movement of the left eye was greatly impaired. The movements downward and inward were impaired. The movement of the right eye was normal. The left masseter and temporal muscles were weak and atrophied and the jaw could be moved only to the left. There was no anesthesia of the face; touch with cotton was somewhat painful. Hearing in the right ear was normal, but the left ear showed a profound nerve deafness. The tongue protruded to the left, its movements were slow, and pronounced atrophy was present on the left side with fibrillary twitchings. The left sternomastoid showed definite atrophy and weakness.

June 5, the gasserian ganglion was exposed for palliative and exploratory purposes. The site of the ganglion was occupied by a large bluish red tumor, of which only a portion 2.5 cm. in diameter was removed. The tumor was believed to be endothelioma on

microscopic examination (Fig. 297). The posterior root was cut. The pain was entirely relieved for one year.

After the patient's dismissal from the Clinic an ulcer of the cornea developed which eventually healed, leaving a dense corneal scar with blindness. In December she had a mild attack of influenza which appeared to have no serious effect, coincidentally with this she lost her voice; a pronounced hoarseness has persisted since.

December, 1919, the patient returned to the Clinic because, during the previous three months, pain had recurred and complete ptosis of the left lid had developed. The pain was now felt not only in the left face but also in the left neck, shoulder, and arm. Besides the ptosis, the left eye was practically without movement, and was blind; the record does not state whether or not light perception was lost. Vision in the right eye was 6/5; the fundus and ocular movements were normal. The anesthesia was total and of typical distribution following section of the posterior root. The left vocal cord was paralyzed, which explained the persistent cough and hoarseness. A few small hard lymph glands were found behind the left lower jaw; they were not removed. These

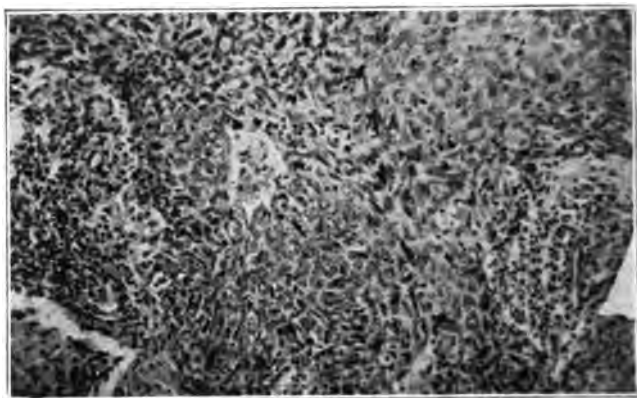


FIG. 297 (Case 3).—Epithelioma (this tumor is indistinguishable from squamous-cell epithelioma of a high degree of malignancy) ($\times 100$).

additional signs indicate that extension of the process had occurred along the middle and posterior fossæ. Only palliative measures were advised.

Case 4 (A213637). Mr. H. M. D., aged twenty-eight years, examined November 13, 1917, had had convulsions during the first two years of his life. When he was four congenital convergent strabismus of the left eye was noticed; he was operated on for this when he was nine. At the age of fifteen the left eye became divergent; this was operated on when he was seventeen. Both eyes have always been prominent, the left more so, and vision in this eye was never sufficient to read by.

Recently, a report was received from the patient's physician, Dr. Otto Lundman of Toledo, and I am including it here in order to continue the narrative of the disease in proper sequence: "In December, 1913 the patient, then in good health, consulted me for refraction. The vision of the right eye with correction was 6/5. With the left eye he counted fingers at two feet. In June, 1914 he returned complaining of dizzy spells when an optic neuritis was found in the right eye and optic atrophy in the left. The visual field was normal in the right eye, but a marked concentric contraction for white

and colors was present in the left. A month later an incipient choked disc was present in the right eye."

The history given in the Mayo Clinic in November, 1917 was that for two years his vision had been failing gradually. Sufficient vision remained to count fingers with the right eye and only to perceive light with the left. Eleven months before, he had noticed a burning prickling sensation on the right cheek, which soon spread to the mucous membrane of the cheek, the right edge of the tongue, the face, and the fore part of the scalp.

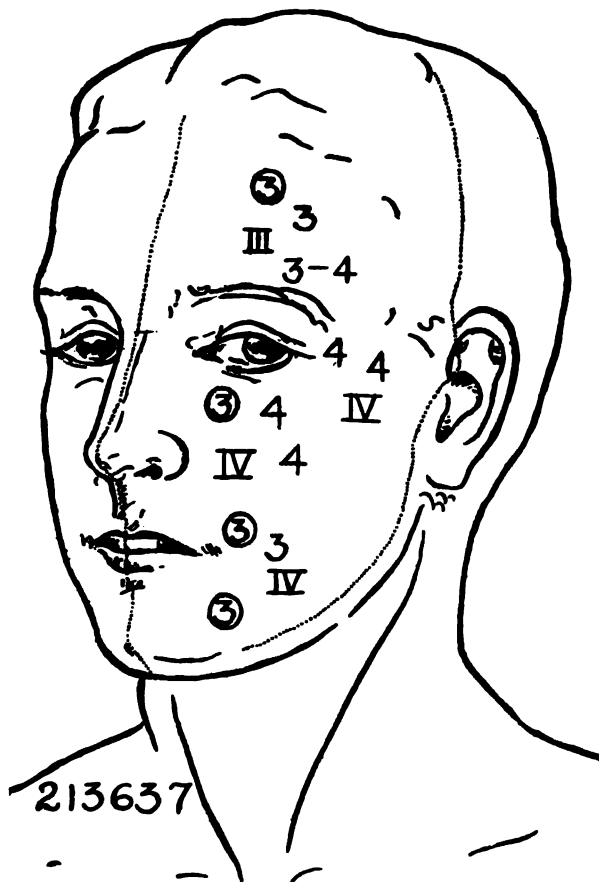


FIG. 298 (Case 4).—Anesthesia chart.

The same area was sensitive to touch and here he sometimes felt sharp shooting pains. Fluids ran from his mouth, nostril, and right eye without his knowledge. His mouth felt as though it were open; his tongue felt rigid. His gait was slightly uncertain, the dexterity of his hands at times was impaired, and occasionally he had spells of dizziness.

The general examination, including blood and spinal fluid tests, was negative. The sella showed some enlargement. The pupils were equal, moderately dilated, and reacted sluggishly to light both direct and crossed. The fundi showed a definite secondary optic

atrophy. There was slight divergence of the left eye and its movements were somewhat impaired, this was attributed to the congenital defect of the ocular muscles.

The sensibility to touch, pain, and temperature was quite uniformly lost over the distribution of the right fifth nerve. The right corneal reflex was absent. The right masseter and temporal muscles were weak and atrophied and the jaw could be deviated only to the right. The patient recognized ammonia in the left nostril, but not in the right. Camphor was detected equally well in both. The hearing was normal to the watch, but the response to the forks was slightly but equally reduced. The neurologic examination was otherwise negative.

November 24, 1917, a well encapsulated reddish blue tumor 2 cm. in diameter, situated above, but involving the right gasserian ganglion, was removed. The tumor was diagnosed glioma on microscopic examination (Figs. 298 and 299). Our observation continued for one month following the operation. Slight subjective improvement in sensation occurred, that is, "he could tell when his lips were closed." The fundus examination revealed a swelling of 2 diopters in each eye, but this subsided. Three and one-half years

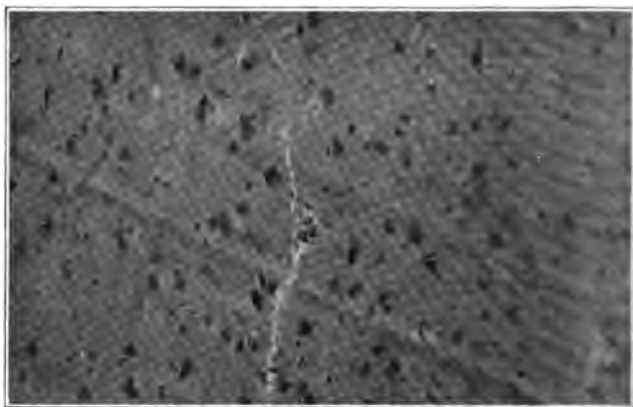


FIG. 299 (Case 4).—Glioma ($\times 100$).

later his physician reported that his general condition is very good. His vision has remained unchanged; the eyes are very prominent. Occasionally sharp pains are felt in the right side of the head, but this is much less frequent than was reported two years before. There is still anesthesia of the right fifth nerve. Thus far no evidence is at hand to indicate a recurrence; in fact, there has been slow, but gradual improvement.

COMMENT

Pain is usually the initial symptom and the one for which relief is sought. It varies considerably in intensity and constancy. Sudden paroxysms of pain were infrequent in our cases and in no instance was it influenced by eating, by speaking, or by external irritation. In three cases the pain was referred to the cheek, lips, chin, or tongue, and in one case it was diffuse over the left face.

Tumors involving the gasserian ganglion exhibited evidence of varied extension into the middle and posterior fossæ. Implication of the nerves immediately adjacent to the ganglion is the rule, but those of the posterior fossa are much less frequently disturbed. Hellsten's patient had atrophy of one-half of the tongue. In Case 2 besides atrophy of the left side of the tongue the patient's left vocal cord was paralyzed and the left sternomastoid was weak and wasted. In Case 3 the patient's tongue and sternomastoid were affected when she was first examined, this was followed in six months by involvement of the left vocal cord. The epileptiform seizures of the patient in Case 2 may have been due to extension of the tumor to the cortex of the temporo-sphenoidal lobe. However, there is no further evidence to support this.

Anesthesia was not demonstrable in the patient in Case 3. The pain was very intense. Sensibility to touch with cotton was acute and somewhat painful. Discrimination of head and point was prompt and accurate. Temperature sensibility was also normal. Spiller reports similar findings in one of his cases, and at necropsy no distinct ganglion tissue was found. This situation is unusual, especially in view of the observation of the surgeon that the gasserian ganglion in Case 3 was completely destroyed by the tumor and that a portion 2.5 cm. in diameter was removed. The ailment had then been of eleven months' duration. Following the cutting of the sensory root a complete permanent anesthesia resulted (at least it was constant for one year) so that the natural progression of the signs was interrupted.

A second peculiarity was found in Case 1 and in Case 2, in that both patients exhibited decided impairment of pain and temperature sensibility over the forehead, while the tactile sensibility was normal in this area in both.

The work of Spiller and others indicates that the spinal root of the fifth nerve serves the sensation of pain and temperature only and that the touch fibers pass work to the sensory nucleus directly after entering the pons. This arrangement of the fibers offers opportunity to damage either group of fibers separately and to abolish either touch or pain and temperature in the corresponding distribution of the fifth nerve.

In Case 1 and in Case 2 touch, pain, and temperature were abolished in the third division, over the second division the touch was moderately impaired, while over the first division it was normal. Over the first division pain and temperature were moderately impaired.

This type of disturbance seems to have been produced by unequal involvement of the ganglion or the peripheral divisions of the nerve.

We had no opportunity other than the limited one offered at operation to study the location and extent of the damage done by these tumors. In Case 2 the cranial nerves were involved from the third to the twelfth nerve, and the bilateral Babinski reaction suggests involvement of the two pyramidal tracts in the same region. There was no impairment of sensation in the trunk or extremities, or any disturbance of gait or station not accounted for by general weakness and emaciation.

The gasserian ganglion may be involved with tumors arising primarily from the nasopharynx. These tumors are usually of the squamous cell type (epitheliomas). In this location the primary tumor may not cause subjective symptoms until the skull is penetrated, when, because of the involvement of one or more of the cranial nerves, the clinical manifestations are those of an intracranial disease. Such tumors may properly come within the scope of this discussion; we have classified them as nasopharyngeal tumors with extension to the central nervous system, although the symptomatology and clinical signs are indistinguishable from those caused by tumors arising within the cranial cavity and involving the ganglion.

We have observed sixty-five tumors of the nasopharynx, nine of which have been attended with intracranial extensions from the optic chiasma to the medulla, and of the nine, four have exhibited the gasserian ganglion syndrome.

In approximately the same period six cases of intracranial tumors involving the ganglion have been observed. One case was reported by Plummer and New in 1913, one patient was not operated on or the case otherwise verified, and four are the cases considered in this paper.

From a therapeutic standpoint the two groups are decidedly different. In spite of the poor prognosis surgical measures are advisable in the intracranial tumors, whereas the tumors of the nasopharyngeal group admit only of palliative treatment with radium; this gives a fair prospect of relief at least from pain.

Involvement of the cervical lymph glands with metastasis from a primary tumor involving the gasserian ganglion has been reported with relative frequency. Metastasis in these glands has no definite localizing value, but is of decisive importance in establishing the presence of malignancy. As nasopharyngeal tumors are even more prone to

metastasize in the cervical glands, this probability should be given due consideration in diagnosis and treatment. Bilateral tuberculous glands was a complication in one case in our series and in two cases small cervical glands, which were noted very late in the clinical course, were left undisturbed because their investigation was of pathologic interest only.

A patient with a tumor involving the left gasserian ganglion is not included in this series, but the case deserves mention because of an associated chronic purulent mastoiditis on the same side. It was thought that extension of the chronic inflammatory process to the dura might involve the ganglion also. A mastoid operation with exposure of the dura, in fact, revealed quite an extensive pachymeningitis, but subsequent complete healing of the operative field failed to modify the symptoms and course of the primary affection. A few weeks later a swelling gradually appeared in the left temple owing to infiltration of the skull by the tumor which precluded any successful intracranial operative procedure. Death occurred one year and four months after onset. No necropsy was made.

Pathologic specimens obtained in Case 1, Case 2, and Case 3 were strikingly similar, as were also the clinical courses. The average duration of life of the three patients after the onset of the symptoms was about two years. Broders states that the present method is to refer to these tumors as endotheliomas, but they are indistinguishable from epitheliomas.

The clinical course in Case 4 is so at variance with the usual course and with that of the average case as to arouse interest. The patient's disease began in 1914 with symptoms of intracranial pressure and optic neuritis. Later secondary optic atrophy began. When he came to us in 1917 for failing vision, the complaint of headache and pain was subordinate and was elicited only after we learned that the optic atrophy was secondary. It is now four years since the tumor was removed. Such great variation in the clinical course indicates a very different type of tumor. The microscopic examination of the fresh tissue at operation and many fixed sections since gave typical pictures of glioma (Broders).

Treatment of tumors involving the gasserian ganglion is beset with many difficulties. The severe and frequent pain which precedes for a long period any objective sign urges one to employ many inadequate measures for relief. The extraction of teeth, exploration of nasal sinuses,

alcohol injections, specific treatment, and the like are used to meet apparent indications with almost uniform failure. It is strange with what frequency unrelated complications, such as syphilis, tuberculosis, or meningitis, are found to be associated with this syndrome. The rarity explains largely the tardiness of recognition even after trustworthy objective signs have appeared. Thus it happens that, although in early operation only can we hope for satisfactory results, surgical interference is generally long delayed. Indeed, it is very doubtful if endotheliomas of the degree of malignancy we have encountered can be successfully dealt with by surgical means.

Section of the sensory root offers relief from pain of variable degree and duration, and it may compensate in some measure for an otherwise futile exploration.

CONCLUSIONS

1. Tumors involving the gasserian ganglion, by marked variation in the rate and extent of growth, display many combinations of signs and symptoms.

2. Anesthesia may not occur, or it may be profound. In two of four cases moderate dissociation of pain and temperature were present.

3. Epitheliomas of the nasopharynx have produced this syndrome with about the same frequency as tumors arising within the skull.

4. Two distinct types of tumor were found. The endotheliomas were malignant and little influenced by surgical treatment. The glioma was benign and produced general symptoms of brain tumor; later it involved the gasserian ganglion. There are no signs of recurrence in this case after three and one-half years.

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CRANIAL NERVE PALSIES PRODUCED BY TUMORS IN THE REGION OF THE JUGULAR FORAMEN*

WILLIAM O. OTT

Three cases of unilateral paralysis of the larynx with involvement of the last four cranial nerves of the same side were selected to report because the paralysis in all of them was due to extracranial tumors. In two cases the paralysis was due to tumors arising from the deep portion of the parotid gland in the retromandibular fossa, and in one case to a lesion in the region of the jugular foramen, the exact nature of which is not known. A tumor was removed by operation in one case only (Case A285410).

Case 1 (A285410). Mr. A. W., aged thirty-five years, came to the Mayo Clinic August 21, 1919, because of deafness in the right ear.

On examination polyps in the right ear and a small mass below the ear were found. The polyps were removed and radium was applied to the mass.

The patient returned to the Clinic October, 1920. He was still deaf and often during fifteen months had had dull pain below the right ear. For eight months he had had headaches in the right temporal region, extending down below the ear, and paresthesia of the right side of the tongue. For one year he had been unable to swallow dry food. He had been hoarse for ten weeks.

Examination revealed the right cord to be fixed, and a collection of mucus in the right pyriform fossa. On neurologic examination the right pupil was found to be somewhat smaller than the left, and the reflexes and fundi negative. There was almost complete motor paralysis of the right half of the soft palate; the right vocal cord was paralyzed and the voice hoarse and nasal. There was moderate paresis of the right sternomastoid muscle, atrophy and fibrillary tremor of the right trapezius muscle, and fibrillary twitchings and slight atrophy and paralysis of the right half of the tongue. A diagnosis was made of paralysis of the ninth, tenth, eleventh, and twelfth cranial nerves with partial paralysis of the sympathetic nerve due to a tumor in the retromandibular space.

November 13, 1920, operation was performed (Adson). The tumor was removed by the technic described herein. The patient recovered uneventfully except for slight weakness of the right facial nerve which was injured during the operation. In a report ten months after operation the patient stated that his voice and the ability to swallow had improved somewhat, but the right half of his tongue was still paralyzed.

Case 2 (A348444). Mrs. N. B., aged forty-two years, came to the Clinic February 3, 1921. She had had ulcer of the stomach fifteen years before; a gastro-enterostomy had

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been performed in 1915, with partial relief of symptoms. She had had migraine with attacks of vomiting and vertigo for about twenty-eight years. For the last eight years she had been partially unconscious during attacks, probably migraine syndrome. For the last six years she had had attacks of choking and coughing; these had been much worse the last two years; occasionally while talking she had a catching sensation in her throat. Her voice was husky and at times lost. The right side of her tongue had felt thick and stiff for about eighteen months.

Examination revealed slight enlargement of the heart to the left with systolic murmur transmitted to the axilla. Examination of the ear was negative. Examination of the blood revealed secondary anemia; the hemoglobin was 30 per cent; the erythrocytes were 3,170,000, the leukocytes 5,800; the differential count was normal. The Wassermann reactions on the blood and the spinal fluid were negative. Roentgenograms of the chest revealed thickened pleura at the right base. Between the angle of the right jaw and the mastoid process was a hard fixed mass. The pharyngeal wall bulged slightly inward posterior to the tonsil on the right. The patient coughed on pressure on the external tumor. Neurologic examination revealed ptosis of the right eyelid, the right pupil smaller than the left, diminished reflex to touch on the right soft palate, partial motor paralysis of the soft palate and pharyngeal muscles, and paralysis and marked atrophy of the right side of the tongue. Speech was slurred and dysarthric. The right vocal cord was completely fixed. There was marked anesthesia over the right half of the soft palate, right pharynx, and larynx. Practically all deep reflexes were increased.

A diagnosis was made of tumor in the region of the jugular foramen, and paralysis involving the ninth, tenth, twelfth, and probably the eleventh nerves. On account of the anemia and the poor condition of the patient radium treatments were given. The patient, in a report seven months after her visit to the Clinic, states that she is somewhat improved, but that the tumor is still present.

Case 3 (A361632). Mrs. G. L., aged forty years, registered at the Clinic June 15, 1921. Seven years before, following the birth of her last child, she noticed slight difficulty in swallowing; this gradually increased and then improved. Six years before she had had occasional occipital headaches. Four years before she had become hoarse and had noticed wasting of the right shoulder and moderate aching of the right side of the neck and back. One year before, her tongue had begun to feel thick and troubled her in speaking. All of her teeth had been removed recently.

The general physical examination, the Wassermann reaction on the blood, and the roentgenograms of the cervical spine were negative. Neurologic examination revealed the pupils, the fundi, and hearing to be normal. The right soft palate was atrophied and paralyzed, the pharynx on the right side was anesthetic. The right sternomastoid and the trapezius muscles were atrophied; the right side of the tongue was atrophied and paralyzed, and the serratus magnus and suprascapular and infrascapular muscles on the right side were atrophied and partially paralyzed. There was a questionable mass in the region below the ear posterior to the ascending ramus of the jaw.

A diagnosis was made of incomplete paralysis of the ninth, tenth, eleventh, and twelfth nerves on the right side and partial atrophy of the supraspinati and infraspinati on the right side, and a lesion in the region of the right jugular foramen. Because of the length of time symptoms had been present and the questionable tumor it was thought inadvisable to explore at this time and radium was applied over the region of the tumor. The patient was dismissed to be observed by her home physician. A report from her October 1 stated that there was no change in her condition.

COMMENT

The recognition of unilateral associated laryngeal paralysis dates from Jackson's first description, in 1864, and since then the condition associated with paralysis of the soft palate and tongue on the same side has been described as Jackson's syndrome. In 1891, Avellis described a group of cases presenting the syndrome of palatolaryngeal hemiplegia. In 1897, Schmidt described still another combination of paralyzes associated with laryngeal hemiplegia. Vernet recently called attention to a combination of unilateral paralysis of the three nerves passing through the posterior lacerated foramen. Collet reported unilateral extracranial paralysis of the last four cranial nerves resulting from injuries. Numerous combinations of unilateral paralysis of the larynx, associated with paralysis of one or more of the last four cranial nerves, may be encountered. Some of these have become classic.

CLASSIC SYNDROMES

	Hemiplegia of larynx.	Hemiplegia of soft palate.	Hemiplegia of tongue.	Hemiplegia of sterno- mastoid and trapezius.
Syndrome of Avellis.....	+	+	-	-
Syndrome of Schmidt.....	+	+	-	+
Syndrome of Jackson.....	+	+	+	-
Syndrome of Topia.....	+	-	+	-
Total syndrome (Collet) of last four cranial nerves.....	+	+	+	+

In Case 1 the last four cranial nerves were involved. Case 2 was similar to Case 1, but the external branch of the spinal accessory nerve was apparently not involved. In Case 3 the last four cranial nerves on the right side were paralyzed, and there was slight atrophy and weakness of the serratus magnus and supraspinatus and infraspinatus muscles on the right side.

It is often difficult to make a diagnosis, and at times it is impossible to differentiate the extracranial lesions of the last four cranial nerves from bulbar or intracranial lesions, but usually in cases of intracranial lesions other symptoms referable to involvement of part of the cerebro-spinal nervous system, such as hemianesthesia, hemiparesis, and hemiataxia are present.

The exact nature of the lesion in many cases reported under Avellis', Schmidt's, and Jackson's syndromes is doubtful, since in many instances

the diagnosis was not verified by operation or necropsy. Some of the verified extracranial lesions which produced unilateral associated laryngeal paralysis were due to aneurisms in the region of the jugular foramen, causing paralysis of the last four cranial nerves. One case was probably the result of tuberculous glands in the retromandibular fossa, producing the syndrome of the posterior lacerated foramen. Many cases were due to trauma, stab wounds, and gunshot wounds in the region of the base of the skull, while others were due to inflammations, nasopharyngeal neoplasms, and syphilitic extracranial lesions. I was unable to find a report of such cranial nerve palsies caused by tumors of the parotid.

TECHNIC OF OPERATION

The method of exposing the region of the jugular foramen in Case 1 was as follows: An incision was made along the anterior border of the sternomastoid muscle, extending well up along the anterior border of



FIG. 300.—Tumor after the sternomastoid had been reflected and before the mastoid process, stylohyoid, and posterior belly of the digastric had been reflected.

the mastoid process. By retracting the anterior border of the sternomastoid backward and by dissecting forward, a well encapsulated tumor was exposed posterior and medial to the ascending ramus of the jaw, and anterior and medial to the mastoid process below the lower bony

wall of the external auditory canal and medial to the stylohyoid and posterior belly of the digastric muscles (Fig. 300). The mastoid process was ronguered away together with part of the temporal bone below the auditory canal. The bellies of the stylohyoid muscle and of the digastric muscle were divided and reflected in order to obtain exposure (Fig. 301). Posteriorly the tumor was in contact with the

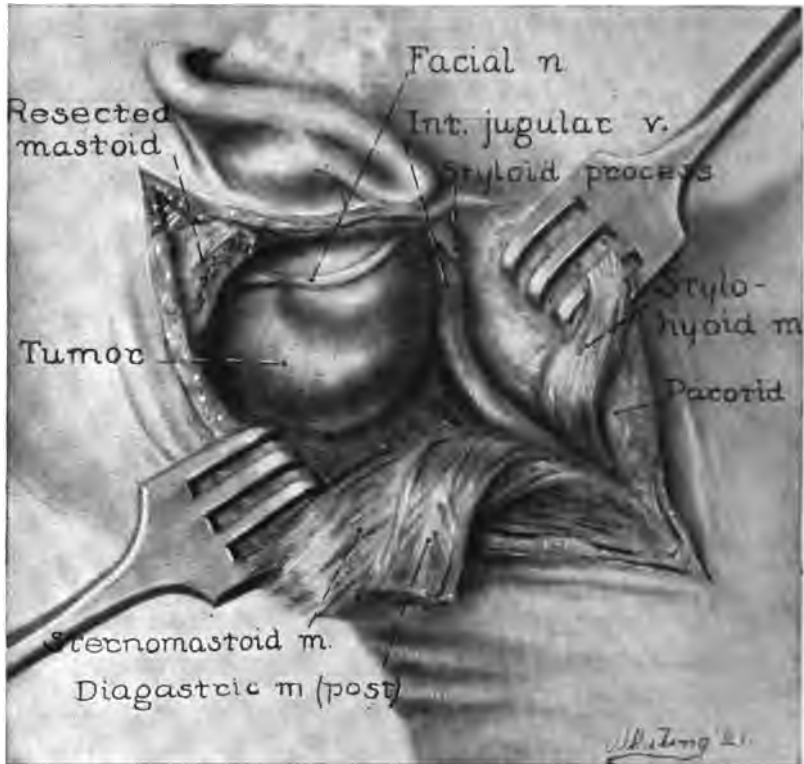


FIG. 301.—The tumor after part of the mastoid process, petrous portion of the temporal bone below the auditory canal, have been ronguered away and the stylohyoid and posterior belly of the digastric muscles reflected.

transverse process of the atlas; it arose apparently from the deep portion of the parotid gland. The ascending ramus of the jaw anteriorly and laterally, and the mastoid process posteriorly, prevented the tumor from bulging outward in its growth, and as a result it pressed against the structures that pass through the jugular foramen (Fig. 302). The tumor was removed by careful dissection, with the capsule intact,

except a small projection which extended up through the jugular foramen along the jugular vein. This part was curetted away, and the

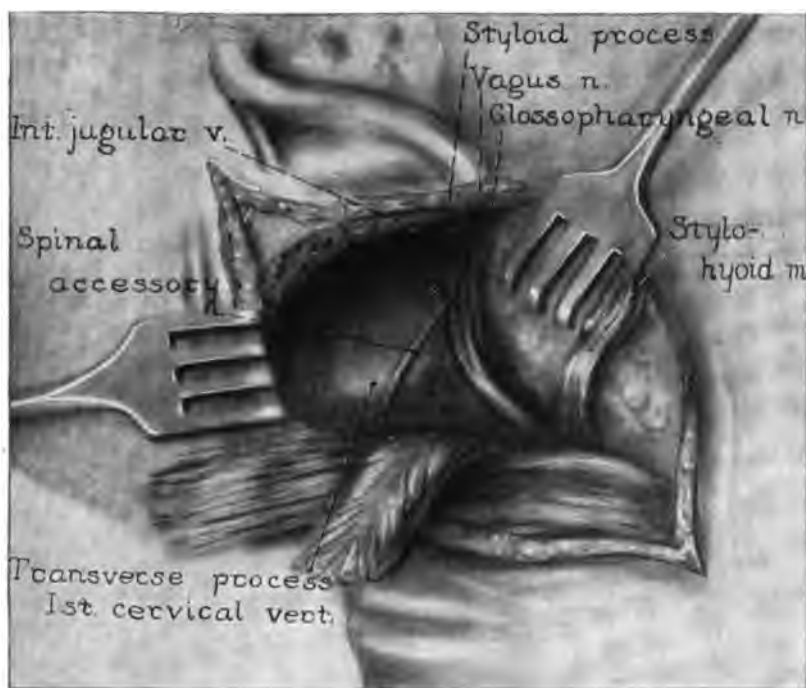


FIG. 302.—The bed of the tumor with the nerves and jugular vein on which pressure had been made by the tumor.

entire cavity packed with gauze saturated in Harrington's solution. Pathologic examination of the tumor revealed mixed tumor of the parotid.

SUMMARY

In the three cases described cranial nerve palsies resulted from tumors in the region of the jugular foramen. In two of the cases the tumor arose from the deep portion of the parotid gland, and in enlarging extended to the region of the jugular foramen. Attention is directed to the fact that extracranial tumors or other lesions in the region of the jugular foramen are accessible and may be removed surgically. If the tumors are of the mixed parotid type, they are encapsulated in the early stages, and during this stage surgical removal is the best method of treatment.

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CEREBROSPINAL ARTERIOSCLEROSIS*

HENRY W. WOLTMAN

Those of us who are fortunate enough to escape death from the multitude of infectious diseases and other accidents to which man is heir will ultimately succumb to a process of disintegration, of which arteriosclerosis of the nervous system is a frequent expression. A case exemplary of this disorder is as follows:

Mr. T. (Case A257266), aged fifty-two years, presented himself at the Clinic January 21, 1919, complaining principally of incontinence, which had been growing worse for two years. Coincident with this was a general failing of strength and the development of a tremor in the legs. One year before he had begun to have dull, heavy headaches and a sensation of having his hat on. His friends noticed that his memory was failing. He left the harnessed horses to stand in the field all night, and forgot to take off their bridles when they were to eat; he expected to dine shortly after a meal was over, and gave his children's ages incorrectly. He became dizzy easily, often fell asleep during the day, and was confused in a crowd. At night he interpreted the rumbling of horses over a nearby bridge as thunder, and often became lost in his own house after he had been lying down.

The Wassermann reaction on the blood was negative. The renal functional tests were normal. The prostate was enlarged slightly; there were slight retinal arteriosclerosis and neurologic evidence of a subacute combined sclerosis of the spinal cord of arteriosclerotic origin.

Arteriosclerosis is not peculiar to old age; it may occur at the age of twenty years. Smith found that deaths occur from cerebral vascular disorders at an average age of sixty years, while apoplexy with hemorrhage and hypertension occurs about ten years earlier. The cause is said to be toxic. Josués first attempted to produce it experimentally by the administration of epinephrin and hydrastin. Saltakow believed he could produce it by the injection of staphylococci. If these experiments are verified, arteriosclerosis may eventually be added to the list of disorders that result from focal infections.

The pathologic changes coincident with arteriosclerosis are generally understood. The difficulty in diagnosis lies in the correlation of such changes with the clinical expression of the disorder.

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Figure 303 is a photograph of some of the larger blood vessels dissected from a brain. The basilar artery, the circle of Willis, the lenticulostriate and lenticulo-optic arteries, the usual site of hemorrhage, are shown clearly. Unfortunately, the athermatous areas are not so well shown; in the basilar artery, however, an enlargement that marks the site of almost complete obstruction of the vessel may be seen. The vessel walls are often greatly thickened (Figs. 304 and 305), particularly the intima, which may ulcerate and liberate emboli, thus causing paralytic strokes. The thickening may eventually completely obliterate



FIG. 303.—Some of the larger blood vessels dissected from a brain showing marked arteriosclerotic changes. The circle of Willis is shown in the center.

the lumen of the vessel. The resorcin-fuchsin stain shows the splitting of the inner elastic membrane. Atrophy and regressive metamorphosis of senility may be seen instead of thickening; the wall of the vessel may become extremely thin and is then ruptured easily.

The lesion in the cord is a diffuse degeneration of the posterior and lateral columns constituting a type of combined sclerosis.

Increased intracellular deposit of pigment is common and has been looked on as a cause of death due to interference with cellular metabolism. A number of such cells may be seen in Figure 306. It would

be more consistent to interpret this as a coincident expression of senescence rather than the cause of it.



FIG. 304.—An arteriosclerotic blood vessel stained with Weigert's elastic stain. Splitting of the inner elastic membrane is shown.

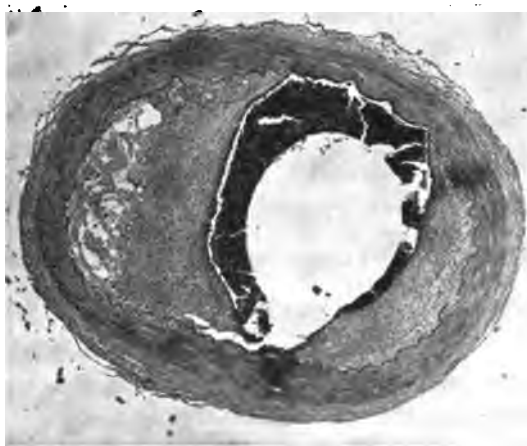


FIG. 305.—Weigert's elastic stain. Cross-section of an anterior cerebral artery showing marked intimal thickening.

One hundred forty-six cases of cerebrospinal arteriosclerosis examined in the Section on Neurology of the Mayo Clinic during the last

year form the basis of my analysis. In 40 per cent of the cases there was objective evidence of spinal cord involvement. Inasmuch as these cases presented also all phases of the cerebral type of involvement, and since evidence of cord involvement strengthens the diagnosis, they were selected for detailed study. The average age of the patients was sixty-three years, the lower and upper extremes were fifty and seventy-eight years respectively. Males predominated (64 per cent). Vertigo was the most common complaint (57 per cent); it was very distressing in 11.8 per cent. Mental impairment was next in frequency. Head-

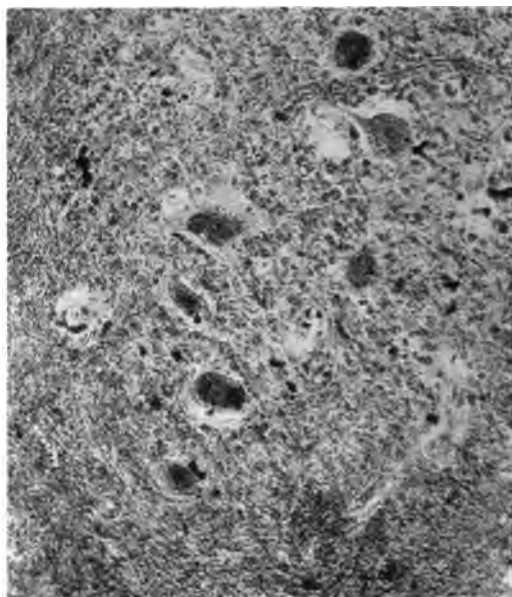


FIG. 306.—Ganglion cells from the spinal cord in a case of arteriosclerosis, stained with Sudan III and methylene-blue. Intracellular deposit of pigment is well shown. One of the ganglion cells near the center of the field is almost normal.

ache was often present and very characteristic. It was often described as a sensation of pressure or weight and was bregmatic or frontal; sometimes it was intense, stabbing, and sharply localized. Patients often complained of trouble in walking; this was usually due to weakness, ataxia, or spasticity. Irritability is considered a common symptom; however, in this series many of the marital partners stated that the patients were decidedly less irritable than they had been during health. Tinnitus is common and furnishes corroborative evidence of wide-spread involvement.

The epilepsy of arteriosclerosis differs in no essential respect from idiopathic epilepsy. Often the attacks are attributed to being "overcome by the heat," although the day may have been relatively cool. One man came because of repeated "sun-strokes." Strokes of various kinds, such as hemianopic, hemiplegic, and aphasic, are severe and incapacitating complications; ordinarily, however, too much importance is attached to them as requisites in making a diagnosis of cerebral arteriosclerosis. They occurred in only 3 per cent of my series.

The diagnosis of cerebral arteriosclerosis does not represent merely an impression based on the history and the general behavior and appearance of the patient. Some help is gained from a careful examination. Pupillary irregularity and poor reactions to light and accommodation may often be noted. Since inspection of pupils has become such an important procedure in the detection of syphilis, the interpretation of pupillary anomalies in senile persons must be made with extreme caution. An examination of the fundus must never be neglected, since retinal arteriosclerosis always means an associated cerebral arteriosclerosis; the reverse, however, is not necessarily true. Hearing, tested with the watch, is often found to be impaired. Patients hear a watch either not at all or at but a few centimeters from the ear. Touch, pain, temperature, and vibratory and joint sensibility may be impaired over the lower portion of the body. The patellar reflexes may be absent or unequal; usually the Achilles' reflexes are either absent or unequal. The abdominal reflexes were absent in 66 per cent of this series. A positive Babinski reflex after one year of age is practically always indicative of an organic lesion of the central nervous system. A finding of the greatest importance, which is manifested in a very striking manner, is poorly sustained attention; this was noted in 62 per cent of patients of the series. The patient must be reminded again and again of the fact that he is being examined and that the point of a pin differs in certain respects from the head. Testing vibratory sensation, which requires full cooperation and fine discrimination, often must be abandoned. The resemblance of symptoms of arteriosclerosis of the nervous system to symptoms of frontal lobe tumors, particularly in the absence of choked discs, is sometimes so striking that differentiation may be quite impossible.

Unlike hemorrhage into the brain, hemorrhage into the cord, or hematomyelia, is rare. It does occur, however, and may cause a clinical picture as follows:

Mrs. A. K. (Case A154978), aged fifty-one years, who had suffered for some time from an extreme hypertension, suddenly developed complete paraplegia. Hot bottles were placed around her lower extremities, and she was very seriously burned and blistered by them before it was discovered that her lower extremities were without sensation. The sphincters were incontinent. The level of the anesthesia reached approximately to the level of the umbilicus. Several secondary infections and bedsores developed and the patient died.

Occasionally the peripheral nerves take part in the process, not nearly so frequently, however, as in pernicious anemia, a fact well demonstrated by Hamilton and Nixon.

Complaints relating to the urinary system are common (Fig. 307). In this series cystoscopic examinations were made when indicated, and trabeculated bladders were found in 8 per cent of the patients. Rectal examinations were made of all, and hypertrophied prostate was found in 8 per cent. Only one patient, however, had an enlargement suffi-

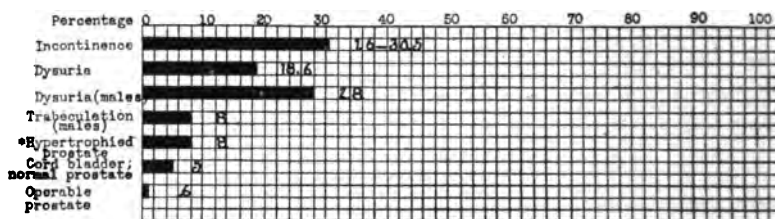


FIG. 307.—Incidents of complaints and findings relating to the urinary apparatus in cases of cerebrospinal arteriosclerosis.

cient to account for the symptoms and the trabeculation of the bladder. Operation in this case was followed by relief of symptoms. Obviously in these cases there is a fine balance between the cord as the cause of the trouble, on the one hand, and the prostate as the cause on the other; both must be taken into consideration, otherwise surgery may be followed by far more distressing symptoms than those for which the patients primarily seek relief.

The relation between high blood pressure and cerebrospinal arteriosclerosis does not appear to be generally understood. The systolic and diastolic blood pressure curves shown in Figure 308 were constructed on differences in pressure of 10 points. Objection is often raised to the diagnosis of cerebral arteriosclerosis on the ground that the blood pressure is normal. The fact remains that 64.4 per cent of patients have a mean pressure of 130 mm. systolic and 78 mm. diastolic. Doubtless the lack of elasticity of vessels is responsible to a large degree

for the low pressures. The same relationship is said to exist in peripheral and in cardiac arteriosclerosis.

In closing, a word might be said with regard to the prognosis. It seems to be the prevailing conception that arteriosclerosis of the nervous system is a terminal condition, and if a patient has been given this diagnosis nothing but death is left for him; and that if he has had one stroke, he has only to await another. It is true that the condition may terminate in this manner, but the patient must not be placed in fear

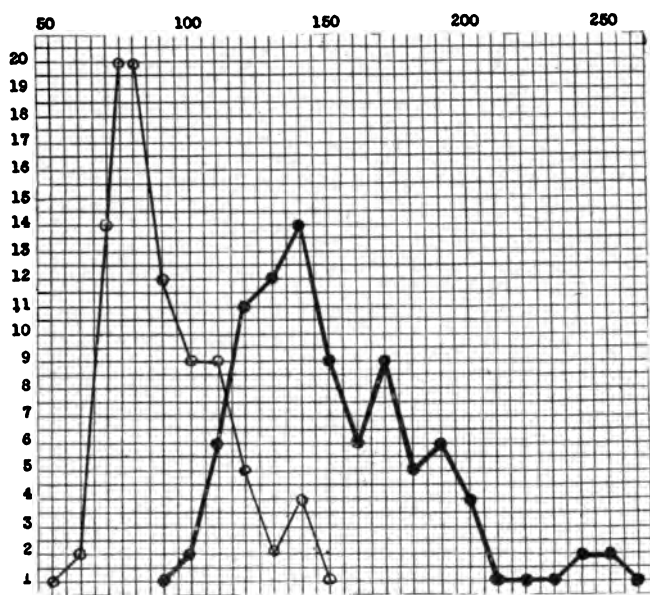


FIG. 308.—Diastolic (light line) and systolic (heavy line) blood pressures in patients having cerebrospinal arteriosclerosis. The number of patients is shown on the left, the blood pressure is indicated above. Practically normal blood pressures are shown in patients with arteriosclerosis of the nervous system.

of expecting every day to be his last. Marked improvement may result if habits of living are corrected, as by a daily noonday nap, and interest in life reawakened.

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IODIN IN THE CEREBROSPINAL FLUID WITH SPECIAL REFERENCE TO IODID THERAPY*

EARL D. OSBORNE

The presence of iodine in the cerebrospinal fluid of normal individuals or of patients receiving iodids therapeutically has hitherto not been demonstrated. Catton, in 1916, reported a series of tests in patients receiving from 15 to 45 grains of potassium iodid by mouth three times a day. He concluded that regardless of the amount of iodine administered by mouth no iodine or compounds of iodine can be found in the spinal fluid, and that either iodine compounds do not pass the ependymal cells of the choroid plexus in any measurable quantity, or such iodine as reaches the spinal fluid is very rapidly fixed in the tissues. These conclusions were based on a method less delicate than that devised by Kendall, which I have employed in this study. This method has enabled me to show that there is iodine in the normal cerebrospinal fluid and that iodine is found in the fluid in increased amounts following its administration by mouth, by rectum, and intravenously. A brief outline of Kendall's method is as follows:

The material is placed in a nickel crucible and evaporated to dryness with sodium hydroxid. It is then fused with solid sodium hydroxid with the addition of potassium nitrate to assist in the oxidation of the organic matter. The fused mass is poured on the crucible cover, and after cooling is dissolved in boiling water on a hot plate. The solution is transferred to a 500 c.c. Erlenmeyer flask and cooled. Five cubic centimeters of a 20 per cent solution of sodium bisulphite and two drops of a 2 per cent solution of methyl orange are added. Eighty-five per cent phosphoric acid is added slowly with constant shaking until the indicator turns pink. Then 5 c.c. of a 20 per cent solution of phosphoric acid is added. This solution is made up to about 250 c.c.; and after placing in it a small piece of hard coal to prevent bumping,

* Reprinted from the Journal of the American Medical Association, 1921, LXXVI, 1384-1386.

it is boiled for at least ten minutes, and then cooled. From five to ten drops of bromin are added and the flask is shaken until the contents assume a definite yellowish color. It is again boiled for just five minutes after the solution becomes colorless. A small amount, from 1 to 2 mg., of salicylic acid is added and the solution cooled. Five cubic centimeters of a reduced 20 per cent solution of phosphoric acid and a few crystals of pure potassium iodid are added. The free iodin liberated is titrated with two-hundredth normal sodium thiosulfate with starch as an indicator. For the numerous details of Kendall's method the reader is referred to his original articles.^{4, 5, 6, 7}

In Table 1 the results obtained with normal spinal fluid are recorded. Five to ten cubic centimeters of spinal fluid were withdrawn from each patient besides the ordinary amount for routine laboratory tests. A mixed spinal fluid from ten to twenty patients was used in each determination. Each patient was carefully questioned with regard to previous therapy, and specimens from those who admitted having had medication by mouth at any time during the preceding three or four months were rejected. Kendall and Richardson found the average iodine content of the blood to be 0.013 mg. per 100 c.c. of blood. My figure of 0.018 for the same amount of spinal fluid is slightly higher (Table 1). This difference, 0.005 mg., is within the range of experimental error and is equivalent to one drop of two-hundredth normal sodium thiosulfate.

POTASSIUM IODID BY MOUTH

In Table 2 are recorded the results obtained after administration of potassium iodid by mouth. In all of the six determinations iodine was found. Necessarily, specimens of spinal fluid from individual cases were in much smaller amounts than 100 c.c. A faint trace was recorded in four cases because in the final titration the amount of two-hundredth normal sodium thiosulfate used was so small that if computed on a scale of 100 c.c. of spinal fluid, the margin of error would be very great. In the other two cases amounts of iodine sufficiently large to be correctly determined were found. These two determinations were made at two and three hour intervals respectively following the administration of the drug. Buckholtz, in 1918, showed that the blood concentration of iodine after administration by mouth was highest from two to three hours after administration. The foregoing determinations suggest a parallelism between the concentration in the blood

and the cerebrospinal fluid. Further study with larger dosages is now in progress.

POTASSIUM IODID BY RECTUM

Two determinations were made on patients receiving potassium iodid by rectum only. The results are recorded in Table 3. Both patients showed appreciable amounts of iodine in the spinal fluid, in the first case 1.808 mg. per 100 c.c. (100 times the normal) one hour after the last administration of the iodid, and in the second case 0.381 mg. per 100 c.c. (twenty times the normal) twelve hours after the last administration.

SODIUM IODID INTRAVENOUSLY

The results obtained at varying intervals following an intravenous injection of 10 per cent sodium iodid solution are shown in Table 4. Iodine in appreciable quantity appears in the spinal fluid within fifteen

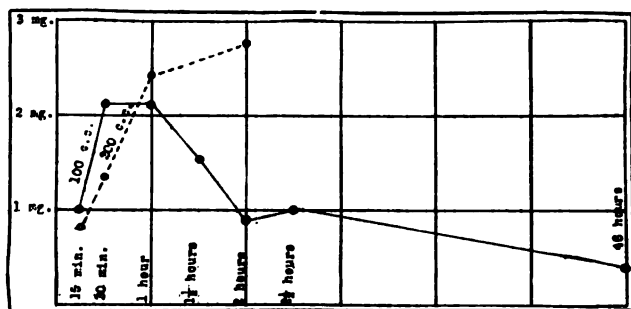


FIG. 309.—Iodine in spinal fluid following sodium iodid intravenously (10 per cent solution).

minutes after the intravenous injection of sodium iodid solution (Fig. 309). With the injection of 100 c.c. of a 10 per cent solution the peak of the curve of increased iodine content of the spinal fluid is reached from one-half to one hour after injection. This amount, 2.133 mg. per 100 c.c., falls rapidly during the next hour, approximately to the same amount as that obtained for the fifteen minute interval. The decline in iodine content is then very gradual until at the end of forty-eight hours 0.4 mg. per 100 c.c. or approximately twenty times the normal content was found. With the injection of 200 c.c. of a 10 per cent solution of sodium iodid the iodine content of the spinal fluid at the end of the one hour interval is only 0.3 mg. per 100 c.c. of spinal fluid, higher than with 100 c.c. However, instead of dropping at this point, the curve continues to rise, and at the two hour interval the

amount of 2.784 mg. per 100 c.c. of spinal fluid is reached. Of necessity these determinations were made by observations on successive patients and not by successive punctures on a single patient.

With large dosages of sodium iodid intravenously the question of a cumulative increase in the amount of the drug must be considered. Very little such increase was observed. One patient received daily intravenous injections of 100 c.c. of a 10 per cent sodium iodid solution for ten days. On the eleventh day he received 200 c.c., and two hours later showed 3.180 mg. of iodine per 100 c.c. of spinal fluid. This amount is approximately only 0.4 mg. higher than that recorded in Table 4 for the iodine content of the spinal fluid two hours after the intravenous injection of 200 c.c. of a 10 per cent solution of sodium iodid in the normal patient.

During the course of the study several observations of especial interest were made which are summarized in Table 5.

Patient A298829 presented a high grade meningeal involvement. His cerebrospinal fluid showed a positive Wassermann reaction, a positive Nonne reaction, and 306 lymphocytes. He was placed on 10 per cent sodium iodid solution intravenously in amounts up to 450 c.c. daily (45 gm.). Twenty-four hours after the last injection the spinal fluid contained 4.851 mg. of iodine per 100 c.c., which is approximately from fifteen to twenty times the amount (0.303 mg.) in 100 c.c. of spinal fluid of a normal patient twenty-four hours after the injection of 200 c.c. of sodium iodid solution (Table 4).

Patient A316534 had advanced *tabes dorsalis* with moderate meningeal involvement which had resisted all efforts at treatment. The Wassermann reaction on the cerebrospinal fluid was positive, the Nonne reaction was negative, and there was one lymphocyte per cubic millimeter. The patient had received 100 c.c. of 10 per cent sodium iodid solution daily for two weeks. Three hours after the last injection he had 4.6 mg. of iodine per 100 c.c. of spinal fluid. As shown in Table 4 the normal amount would have been about 1 mg. per 100 c.c.

Patient A250805 had an even more marked meningeal syphilis. In spite of all treatment, the cell count on the spinal fluid varied from 149 lymphocytes at the time of examination to 110 lymphocytes and 306 polymorphonuclears at the time of the test. He had received daily injections of from 100 to 250 c.c. of the sodium iodid solution. His spinal fluid contained 42.3 mg. of iodine per 100 c.c. This amount

is about thirty times more than what would be expected under similar conditions in a patient without evidence of neurosyphilis.

Patient A334068 presented well advanced *tabes dorsalis* with very slight meningeal involvement. The spinal fluid Wassermann reaction and the Nonne reaction were positive; there was one lymphocyte. Two hours after an intravenous injection of 200 c.c. of a 10 per cent solution of sodium iodid the spinal fluid contained 4.377 mg. per 100 c.c. as compared with the normal amount of 2.784 mg. under the same conditions. These four observations point to one or both of two possibilities; either the meninges are more permeable to iodine compounds when there is meningitis, or tissue actively involved by syphilis takes up more iodine than normal tissue. Loeb, in 1912-1913, found that iodids accumulated in greater concentrations in syphilitic glands than elsewhere in the body, suggesting a selective affinity for syphilitic processes. Fujisawa, in 1919, made the statement that all syphilitic tissue takes up more iodine than other organs. My observations tend to support the latter possibility. In Patient A298829, moreover, the determination was made twenty-four hours after the last intravenous injection which indicates that the iodine had been fixed in the syphilitic tissue, thus causing an increased concentration in the spinal fluid. In Patient A316534 there was only a mild meningeal involvement. Neurologic examination revealed a far advanced parenchymatous degeneration of the posterior columns. This suggests that the large amount of syphilitic tissue had fixed a correspondingly large amount of iodine. In Patient A250805, however, the process was predominantly meningeal, pointing to an increased permeability of the meninges. Patient A334068 presented essentially the same condition as Patient A316534 except that he had practically no active meningeal involvement.

The foregoing data suggest the possibility that the iodine content of the cerebrospinal fluid following iodine administration may be of diagnostic importance in the study of diseases of the central nervous system.

CONCLUSIONS

1. Iodine is present in the cerebrospinal fluid of normal individuals.
2. Iodine, in increased amounts, is present in the cerebrospinal fluid following the administration of iodids by mouth, by rectum, and intravenously.

3. The iodine content of the cerebrospinal fluid following administration of iodid by mouth or by rectum is small compared with that following the administration intravenously.

4. The iodine content of the cerebrospinal fluid following the administration of iodid intravenously plots a definite curve, depending on the amount administered.

5. Certain observations made in the course of this study suggest the possibility that (a) neurosyphilitic tissue takes up more iodine than normal nervous tissue, and (b) the presence of meningitis increases the permeability of the meninges to iodine compounds in the blood.

TABLE 1
IODIN IN NORMAL SPINAL FLUID

Spinal fluid, c.c.	Iodin in spinal fluid, mg. in 100 c.c.
100.....	0.002
100.....	0.022
100.....	0.019
75.....	0.024
100.....	0.019
100.....	0.018
100.....	0.020
100.....	0.021
100.....	0.019
Average.....	0.018

TABLE 2
IODIN IN SPINAL FLUID AFTER ORAL ADMINISTRATION OF POTASSIUM IODID

Spinal fluid, c.c.	Potassium iodid three times a day.	Iodin in spinal fluid, mg. in 100 c.c.
10	50 grains last dose three hours before.	Faint trace*
10	100 grains last dose twelve hours before.	Faint trace*
10	100 grains last dose two hours before	Faint trace*
7	50 grains last dose two hours before.	0.357
15	50 grains last dose seventy-two hours before.	Faint trace*
15	70 grains last dose three hours before.	0.385

* Amount too small to be accurately titrated.

TABLE 3
IODIN OF SPINAL FLUID AFTER RECTAL ADMINISTRATION OF POTASSIUM IODID

Spinal fluid, c.c.	Potassium iodid three times a day.	Iodin in spinal fluid, mg.
5	125 grains last dose one hour before.	1.808
10	350 grains* last dose twelve hours before.	0.381

* Impossible to estimate exact amount retained, probably not more than 50 per cent.

TABLE 4
IODIN IN NORMAL SPINAL FLUID AFTER INTRAVENOUS ADMINISTRATION OF 10 PER CENT SODIUM IODID SOLUTION

Spinal fluid, c.c.	Sodium iodid, c.c.	Hours before spinal puncture.	Iodin in spinal fluid, mg. in 100 c.c.
15	100	One-fourth.	1.00
15	100	One-half.	2.133
15	100	One.	2.133
15	100	One and one-half.	1.533
15	100	Two.	0.900
15	100	Two and one-half.	1.033
10	100	Forty-eight.	0.400
15	200	One-fourth.	0.804
15	200	One-half.	1.341
10	200	One.	2.414
15	200	Two.	2.784
8	200	Twenty-four.	0.303

TABLE 5
SPECIAL OBSERVATIONS

Case.	Diagnosis.	Following 10 per cent sodium iodid.	Amount of last injection, c.c.	Hours before spinal puncture.	Iodin in spinal fluid, mg. in 100 c.c.
A298829	Neurosyphilis; marked meningeal involvement.	200 to 400 c.c. daily for two weeks.	450	Twenty-four.	4.851
A316534	Neurosyphilis; advanced tabes dorsalis.	100 c.c. daily for two weeks.	100	Three.	4.600
A250805	Neurosyphilis; marked meningeal involvement.	100 to 250 c.c. daily for two weeks.	250	One-half.	42.308
A334068	Neurosyphilis; advanced tabes dorsalis.	None.	200	Two.	4.377

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THE GROSS PATHOLOGY OF BRACHIAL PLEXUS INJURIES*

ALFRED W. ADSON

The numerous unsatisfactory results obtained from the treatment of brachial plexus paralysis stimulated me to carry out an experimental study of the gross pathology of the various types of brachial plexus injuries by attempting to produce on cadavers two or three hours after death an injury equivalent to that received in life.

In reviewing the literature two distinct views were noticed with regard to the etiology of brachial plexus paralysis: first, that the injury is primarily of the brachial plexus, and second, that it is primarily of the shoulder joint and the brachial paralysis a subsequent result. Duchenne, in 1872, first called attention to birth palsies. He described paralysis of the newborn with an involvement of the fifth and sixth cervical roots. Erb, in 1874, described paralysis of the brachial plexus, traumatic in origin, which he stated was identical with the Duchenne obstetric birth palsy, a lesion of the fifth and sixth cervical roots. These lesions have been found to coincide with lesions found by Taylor and Casamajor and Thomas, except that the paralysis at first was complete and the arm hung as a flaccid extremity; this gradually improved and left an involvement of the fifth and sixth cervical roots. Taylor and Thomas are the two principal exponents of these views, and numerous articles and cases have been presented by both.

Taylor and Casamajor, in 1913, reported six cases of "traumatic Erb's paralysis," in which the paralysis was due to a separation of the upper roots. It was their belief that the roots were lacerated in order from the fifth cervical downward, the cervical fascia being the first structure to tear, next the nerve sheaths, the nerve itself, and finally the blood vessels, producing hematomas, which were followed by inflammatory reaction and scar tissue. Five patients were operated on with not highly gratifying results. Aside from the removal of the scar tissue, end-to-end anastomosis and nerve bridging were advised;

* Reprinted from *Surgery, Gynecology and Obstetrics*, 1922, xxxiv, 351-357.

the two latter procedures have not been very satisfactory in the repair of peripheral nerves. In 1913, Taylor reported a series of cases and stated that it is difficult to operate on intraspinal injuries and injuries of the roots close to the intervertebral canal, and that little benefit can be expected. The subluxation that occurs is, in his opinion, the result of an infantile condition of the clavicle, scapula, and humerus with a marked subsequent traumatic neuritis. Massage and passive motion aggravate the condition, and even though surgery does not offer a great deal, it is the best means of relief. In 1920, Taylor stated that patients with obstetric birth palsy seldom recover completely, as is maintained by the pediatrician and the neurologist, and while surgical treatment brings about some improvement, too much should not be expected of it. Spontaneous recovery should be looked for during the first three months only. Taylor reports having operated on seventy patients with only three deaths, and of having seen in consultation 130 additional patients not operated on. Only ten of these patients were under two months of age.

In October, 1910, Thomas presented a paper on the laceration of the axillary portion of the capsule of the shoulder joint as a factor in the etiology of traumatic combined paralysis of the upper extremity. He stated that birth palsy is due to the influence of scar tissue following effusion of blood and synovial fluid from a lacerated capsule of the shoulder joint with subluxation. This article was supplemented, in 1916, by one in which he stated that the general surgeon usually ascribes the lesion to an injury of the brachial plexus, and ignores the ankylosis and pain at the shoulder; he referred to Duchenne's article in which four cases were reported of posterior subluxation of the shoulder and of internal rotation with paralysis. Thomas further states that Duchenne, in 1872, in his third edition, reported four other subluxations, but Thomas believes that still other subluxations were overlooked. He states that when a palsy is due to an injury in the region of the shoulder and is associated with ankylosis of a shoulder joint, it disappears with the restoration of the normal motion to the shoulder joint, that the injury to the plexus must be due to injury of the joint, that perfect recovery will take place by the aid of exercise, provided there is no displacement. In most chronic cases posterior subluxation with an internal rotation is found, and he suggests a reduction of the shoulder joint, if possible, by manipulation, otherwise by operative procedure with abduction of the arm. In 1917, Thomas again empha-

sized that brachial paralysis in most cases is secondary to joint injury and that it disappears with a complete recovery of the joint injury. Nerve lesions with stiff and painful joints recover without surgery and the repair of flail joints and the reduction of dislocations place the lesion in this former group in which recovery takes place. In 1920, Thomas reported eighteen cases of injury to the shoulder, in twelve of which operation was performed. In nine the paralysis disappeared, in two it is disappearing; one of the patients died. Besides these eighteen cases he has seen forty-four birth palsies, which he had reported, in 1914, as pseudopalsies. He continues to adhere to his original contention that "on the normal side the upper end of the humerus projects a variable distance in front of the anterior edge of the acromion. On the side of subluxation it cannot be felt from in front, and by careful palpation with the finger the anterior edge of the acromion can be located a considerable distance below its normal level. On the normal side there is a hollow under the posterior border of the acromion; on the affected side, a prominence."

In 1908, Schultz reported fifty-four uncomplicated cases of shoulder dislocation. Paralysis developed in varying degrees in 75 per cent of his patients. There were no brachial nerve complications at the time of the injury; the lesions developed subsequently, which is contrary to the manifestations in cases of classical obstetric birth palsies or brachial plexus injuries in which the paralysis is frequently complete for several weeks and then improves and is limited to certain roots.

Fioux, in 1897, found experimentally that he was able to tear the brachial roots by forcible separation of the head and shoulder in the cadaver.

Delbet and Cauchoix, in 1910, collected thirty-five cases of brachial plexus injury from necropsy findings and surgical reports, and in none of these was a distinct rupture found; in every instance, however, there was extravasation of blood and inflammatory and cicatricial tissue. Taylor reported twenty dissections on ten infant cadavers, three to ten days after birth, and found that tension was the only factor in the production of the lesion. Thomas applied forceps to the cadavers of six babies and was unable to rupture the brachial plexus by traction.

A review of the literature shows that injuries in obstetric birth palsies involve the fifth and sixth roots more frequently than the others, that the injuries are very slight in some cases, and that rarely, if ever, a complete laceration of the root occurred. Examination of

the plexus shortly after birth discloses very little, but if the paralysis is permitted to continue for several months a mass of scar tissue close to the roots probably with involvement of the roots is found. The presence of scar tissue so remote from the shoulder and axilla leads one to believe that the scar tissue is a result of injury to the cervical fascia, epineurium, perineurium, and the rupture of blood vessels and fasciculi. While subluxations occur, particularly in breech presentations, and in cases in which extreme abduction of the arm is necessary, many dislocations in chronic birth palsy no doubt are the subsequent result of the infantile development of the shoulder joint.

A study of 101 cases of brachial plexus injuries observed at the Mayo Clinic, forty-five of which were birth palsies and fifty-six brachial plexus injuries due to direct blows on the plexus over the shoulder, associated in some instances with fractures and dislocations, falls, severe torsion, and gunshot and stab wounds with varying degrees of paralysis, leads me to believe that the treatment of brachial plexus injuries depends on the cause and the degree of the injury, and that no one method, medical, neurologic, or orthopedic, should be used as a panacea for all brachial plexus injuries.

EXPERIMENTAL STUDY

Since my material was insufficient for a study of obstetric birth palsy immediately following the injury and the death of the patient, an attempt was made to reproduce experimentally five groups of injuries of the plexus due to trauma of the neck and shoulder.

I first attempted to produce the injuries on the fresh cadaver by applying traction and torsion on the arm and shoulder in various directions, without exposing the brachial plexus, and by applying approximately 150 pounds pull. Dissections of the brachial plexus and shoulder were then made, but grossly no pathologic condition was found. After the brachial plexus had been dissected free, exposing the fifth, sixth, seventh, and eighth cervical and the first thoracic roots, the upper middle and lower trunks, and the outer, inner, and posterior cords, the same pull was applied again, demonstrating which portions of the plexus were under the greatest strain. It was observed that if the pull was made gradually the tissues composing the nerve root, trunk, and cord would withstand greater force than if the pull was made with a jerk, giving proof that the fascial attachments connected with the nerve sheaths aid in the protection of the nerve roots and trunk,

and that the torsion pull and upward traction place a great strain on the muscles and ligaments at the shoulder so that it is readily understandable why injuries severe enough to injure the brachial plexus would also produce dislocations and fractures near the shoulder. Injuries produced by the downward pull with a forcible separation of the head and neck and by the oblique outward downward pull resulted in very little injury to the shoulder. As the experiments were repeated from time to time it became evident that practically the same types of injuries took place in precisely the same manner so far as avulsions and lacerations were concerned.

Group 1.—The experimental injuries of Group 1 represent an accidental injury in which the pull is downward and outward, as when the hand is caught and a sudden attempt is made to release it by jerking away. The tension was equally distributed over the nerve roots, trunks, and cord; the first structure to break was the fascial sheath; the second, the blood vessels about the cord distal to the nerve trunk. After stretching and lacerating the nerve sheaths a narrowing of the brachial cords was noted; as further tension was applied more laceration in the epineurium was produced with breaking of the fasciculi, until finally there was a complete elongated laceration distal to the nerve trunk in the three cords. This particular type of injury was significant inasmuch as it spread over a distance of from 8 to 10 cm., that is, the fasciculi broke at various levels under different degrees of tension and when the laceration was complete a group of attenuated fibers was present. It also illustrated that when the pull was equally distributed over all of the nerve roots, trunks, and cords, the gross injury was not near the intervertebral canal, but distal to the brachial cords, thus making the surgical repair very difficult since resection of approximately 8 to 10 cm. would be necessary before all of the fibers could be found in cross sections. In addition, there was marked injury to the fasciculi throughout their entire course above and below the site of the complete laceration. After the injury had been produced the bodies of the fourth, fifth, sixth, and seventh cervical and first and second thoracic vertebræ were removed, and the cervical cord with the roots and ganglia were lifted out so that a more extensive study could be made. The findings already obtained were corroborated (Fig. 310).

Group 2.—The experimental injuries of Group 2 represent an injury produced by forward torsion with traction, as in belt injuries, in which the hand or arm is caught and rotated forward. Tension was

first applied over the cervical fascia around the cervical roots, particularly to the seventh cervical root; the latter was the first to give way, next the epineurium, and last the fasciculi, with complete division distal to the spinal ganglion, but proximal to the nerve trunk. As the tension was increased, the first thoracic and eighth cervical roots showed evidence of involvement, followed by the sixth and then the fifth cervical roots. This is of significance on account of the particular involvement of the seventh cervical root, and is probably accounted for by the fact that the seventh cervical root is the shortest of all of the roots making up the cervical trunks of the brachial plexus. Non-avulsion of the ganglion with laceration of the root outside the intervertebral canal is probably accounted for by the fact that even though

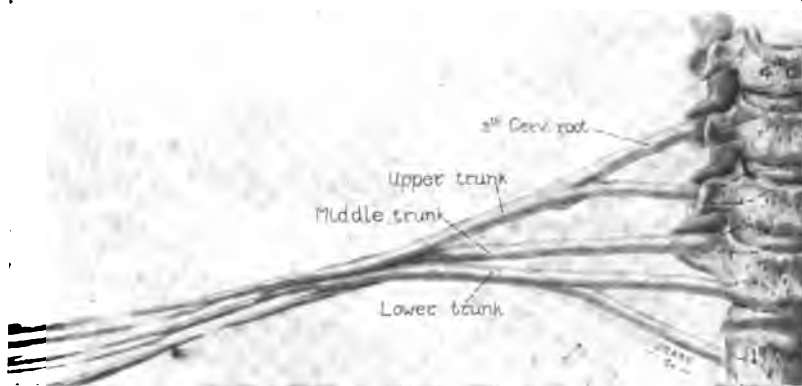


FIG. 310.—An elongated laceration of the brachial cords and peripheral nerves produced by a downward outward pull on the brachial plexus.

the tension is greatest on the seventh cervical root, it is also distributed over the eighth cervical root and the first thoracic root. In jerk injuries in which all the tension was practically on one root, avulsion of the ganglion and spinal root usually took place; the fascia over the ganglion of the seventh, eighth, and first thoracic roots was frequently lacerated, which resulted in an inflammatory reaction and scarring, and accounted for the severe pain experienced in brachial plexus injuries (Fig. 311).

Group 3.—The experimental injuries of Group 3 represent injuries similar to those produced by forward torsion with traction in which the hand or arm is rotated backward. The first effect of the injury was on the first thoracic root; the fascia and epineurium became lacerated; this was followed by complete laceration of the roots between

the ganglion and the lower brachial trunk, laceration of the fascia around the ganglion with partial avulsion of the ganglion, considerable tension



FIG. 311.—Laceration of the seventh cervical nerve root with partial laceration of the fascia and fasciculi of the eighth cervical and first thoracic nerve roots produced by forward torsion with traction on the brachial plexus.



FIG. 312.—Laceration of the first thoracic nerve root with partial avulsion of the ganglion and partial laceration of the eighth cervical and seventh cervical nerve roots with partial avulsion of the ganglion of each produced by backward torsion with traction.

on the fascia around the root of the eighth cervical nerve, and slight tension on the fascia around the root of the seventh cervical nerve. Increased rotation and traction resulted in avulsion of the ganglion

and spinal roots of the eighth and seventh cervical nerve roots and partial avulsion of the sixth cervical ganglion. These results again emphasize that the injury is not abrupt and confined to one place, but that tension applied to a particular root may produce not only laceration of the nerve roots but also partial or complete avulsion of the ganglion and spinal root. In some instances the spinal roots break between the ganglion and the spinal cord; in other instances they pull out of the spinal cord, thus illustrating how difficult and unsatisfactory operations are in this type of injury, which may be just distal to the ganglion or in it, or between the ganglion and the cords, or perhaps in



FIG. 313.—Laceration of the first thoracic nerve root with partial avulsion of the ganglion and partial lacerations of the eighth cervical, seventh cervical, and sixth cervical nerve roots with complete avulsion of the ganglion of the eighth cervical and seventh cervical, and partial avulsion of the ganglion of the sixth cervical nerve roots produced by exaggerated backward torsion and traction.

the cord itself. Horner's syndrome is frequently produced by this group of injuries (Figs. 312 and 313).

Group 4.—The experimental injuries of Group 4 represent injuries produced by forcible downward traction of the shoulder with counter-traction on the head and neck such as is caused by blows, by falling objects, or by a person being thrown from a vehicle and striking on the tip of the shoulder and side of the head. Falling objects striking midway between the shoulder and the head may produce injuries of the fifth, sixth, and seventh cervical roots of the plexus. These injuries simulate to a great extent those of the external popliteal nerve as it

passes over the fibula or those of the ulnar nerve at the elbow. While the continuity of the nerve may be left undisturbed, the injury may be severe enough to destroy the blood vessels and axons, causing inflammatory reaction and considerable scar tissue. In the experiments the forcible downward pull usually resulted in laceration of the cervical fascia, epineurium, and blood supply before there was much apparent injury to the fasciculi. As the tension was increased, however, complete laceration of the fifth cervical root took place between the ganglion and the nerve trunks, in addition to partial avulsion of the ganglion and



FIG. 314.—*a*, Laceration of the fifth cervical nerve root and partial avulsion of the ganglion and tension on the sixth cervical nerve root produced by forcible downward traction of the shoulder with countertraction of the head. *b*, With increase in tension the result is complete laceration of the fifth cervical nerve root with partial avulsion of the ganglion, and partial laceration of the sixth, seventh, and eighth cervical nerve roots, with complete avulsion of the ganglia of the sixth and seventh cervical nerve roots and partial avulsion of the ganglion of the eighth cervical nerve root.

spinal roots. A further increase in tension brought about injury to the sixth cervical root, to the seventh cervical root, as well as moderate injury to the eighth cervical and first thoracic roots, and resulted in avulsion of the ganglion, laceration of the spinal roots of the sixth and seventh cervical roots, and injury to the fascia of the eighth cervical roots. This injury illustrates the result of tension applied principally to the various roots in order from above downward; it is the most common of the Erb-Duchenne paralysis, usually spoken of as obstetric birth palsy. The degree of tension determines the extent of injury (Fig. 314, *a* and *b*).

Group 5.—The experimental injuries of Group 5 represent injuries produced by forcible upward and backward traction when the body falls downward and the arm and shoulder are suddenly jerked upward in an attempt to break the fall. The results were a tear of the fascia at the ganglion of the first thoracic root in the intervertebral foramen, avulsion of the ganglion and the spinal roots of the first thoracic and eighth cervical roots, laceration of the sheaths in the seventh cervical roots distal to the ganglion, moderate laceration of the sixth and fifth cervical roots, and partial laceration of the communicating sympathetic



FIG. 315.—Partial laceration of the first thoracic, eighth cervical, and seventh cervical nerve roots with complete avulsion of the ganglia of the first thoracic nerve root and the eighth cervical nerve root and partial laceration of the sympathetic connection with the first thoracic ganglion produced by forcible upward and backward traction.

branches which are attached to the spinal ganglion of the first thoracic. This injury is also productive of Horner's syndrome, and is further confirmatory of the facts that involvement of the first thoracic root results in the production of this syndrome and that when injuries are confined chiefly to one root they result in laceration of the sheaths at the nerve root and ganglion with partial or complete avulsion of the ganglion.

Gunshot and stab wounds of the brachial plexus are very much similar to those of peripheral nerves except perhaps that the extravasation of blood and the formation of scar tissue may result in the

involvement of nerves other than those directly injured. The treatment followed in cases of peripheral nerve injury is indicated (Fig. 315).

SUMMARY

1. Injuries of the brachial plexus, except those described under Group 1, are situated in the vicinity of the intervertebral canal proximal to the brachial trunk.

2. The injuries may be slight, lacerating only the fascia around the cervical roots, or they may be severe and result in laceration of the cervical roots between the cervical ganglion and the cervical trunk, with or without avulsions of the ganglion.

3. Inasmuch as injuries of the brachial plexus are produced in the root or the ganglion, they seem primarily to be lesions of the nerve rather than secondary to lesions of the shoulder joint.

4. Patients with milder injuries may be expected partially or completely to recover without surgical treatment, but those with more severe injuries rarely recover, even with surgical treatment.

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TREATMENT OF SCIATICA: A STUDY OF THIRTY-FOUR CASES TREATED BY EPIDURAL INJECTIONS AND REMOVAL OF FOCI OF INFECTION*

WILLIAM O. OTT

The results of treatment by epidural injections of saline solution containing novocain and the removal of foci of infection in thirty-four cases of sciatica observed in the Mayo Clinic during a period of two and one-half years form the basis of this study.

I have not attempted to classify the cases into sciatic neuritis and sciatic neuralgia, for such a classification is not always possible. Cases in which the sciatic pain could be attributed definitely to some bony condition and cases in which doubtful diagnoses were made have been eliminated from the report.

It will be noted that pain along the sciatic nerve is the most common subjective symptom, being present in all the cases. Pain in the sacro-iliac region was present in 94 per cent of the patients, backache on the same side in 68 per cent, and backache on the opposite side in 29 per cent. Bilateral sciatica was present in two patients (6 per cent). Tenderness over the sciatic trunk was a constant objective finding.

The bony changes were not marked; in none of these cases were they demonstrated to be a cause in producing the sciatica.

After all the palpable causes of sciatica, such as malignant growths pressing on the lumbar sacral plexus, subluxation of the sacro-iliac joint, syphilis, diabetes mellitus, pelvic tumors, and so forth, have been eliminated, there still remains a large group, perhaps the larger group of cases of sciatica, in which infection must be looked on as the cause of the pain. The exact seat of the pathologic process is not always determinable. Dejerine and his school classify sciatica into neuritis of the trunk and neuritis of the roots. The fact that 94 per cent of the patients experienced pain over the sciatic distribution down the

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TABLE 1
PRINCIPAL SYMPTOM: PAIN

	Patients.
Sciatic nerve distribution.....	34 (100 per cent)
Sacro-iliac region.....	32 (94 per cent)
Lumbar region (same side).....	27
More or less constant.....	20
Definite attacks with free intervals.....	14

POSSIBLE ETIOLOGIC FACTORS

	Patients.
Strain or wrench of back.....	9
Acute infection.....	6
Exacerbation of sciatica (chronic cases) with colds.....	5
Occupation.....	3

PHYSICAL AND ROENTGENOGRAPHIC FINDINGS

	Patients.
Lasègue's sign positive (94 per cent).....	32
Tenderness over trunk of sciatic nerve (88 per cent).....	30
Achilles' reflex diminished or absent (50 per cent).....	17
Atrophy of muscles of affected extremity (38 per cent).....	13
Some limitation of motion in the spine.....	9
Hypertrophic arthritis of the lumbar spine.....	3
Sacro-iliac disease (?).....	2
Hypertrophic arthritic hip.....	1
Lesion of fourth and fifth lumbar vertebrae (character doubtful).....	1
Old healed fracture of the femur.....	1
Sacralization of the fifth lumbar vertebrae.....	1

affected leg during the epidural injections, and not on the opposite side, is evidence that either the roots or the ganglia were hypersensitive compared with those of the unaffected side. The pressure of the fluid can come in contact only with the root covered by the fold of dura, or with the ganglia in the foramina and slightly beyond, as was shown by dissection of a recently dead body in which 60 c.c. of methylene-blue were injected into the epidural space. The fluid passed epidurally to the upper cervical region. In fact, there was as much fluid in the cervical region as in the lumbar region. The fluid passed to the outer edge of the ganglia to the point where the dorsal nerves are given off, but slightly farther distally in the sacral region. None of the fluid reached the subdural or subarachnoid spaces. Were the inflammation located

exclusively distal to the ganglia, pain from the pressure of the fluid only should not be experienced down the affected leg. Interstitial fibrosis and thickening of the sheath of the sciatic trunk have been described, but I have been unable to find reports of careful histologic studies of the roots and ganglia in patients with sciatica coming to necropsy. As yet knowledge of the pathologic changes and the location of the lesion in the so-called idiopathic sciatica is incomplete. In view of the fact that the greater percentage of the cases in this series were caused by infectious processes either directly affecting the roots, ganglia, or trunk of the sciatic nerve, or by toxic products from infection elsewhere in the body which caused deleterious changes in some of these structures, it is considered important to remove all possible foci of infection. Fourteen of the thirty-four patients had infected tonsils for which tonsillectomies were performed. Twenty-three patients had foci of infection around the teeth and the teeth were removed, or removal was recommended.

The technic of epidural injection for sciatica is simple. It has been described quite fully by Cathelin, Strauss, and others. A 10 c.c. Luer syringe with an ordinary spinal puncture needle is used. The needle is introduced into the sacral canal for from 5 to 6 cm. Care is taken not to introduce it farther, since there is danger that the spinal subdural space may be entered because of the reflection in most persons of the dural sheath around the upper margin of the second sacral vertebra. After the introduction of the needle the trocar is removed and suction made with the syringe in order to be sure that no cerebrospinal fluid escapes. If it does, the needle is withdrawn for 2 or 3 cm. The solution used in the Mayo Clinic usually is 0.5 per cent novocain in physiologic salt solution. The solution is introduced very slowly; for from ten to twenty minutes is necessary for the injection of from 40 to 50 c.c. Ordinarily 50 c.c. is sufficient. The injections may be repeated every forty-eight hours if relief is not obtained. At times seven or eight injections may be required. It has been our experience that after the first injection the pain is in most cases relieved entirely for from two to three hours and ameliorated for the next two to ten days, and the patient enjoys a full night's rest.

Of the thirty-four patients treated by epidural injections, fourteen received one injection, thirteen two injections, four three injections, two four injections, and one five injections. Nine patients received complete and permanent relief; fourteen received partial relief, which

allowed them to return to work; eleven did not receive permanent benefit from the injection. Temporary relief, that is, for from two days to two weeks, either complete or partial, was obtained by thirty-one patients.

In the greater number of cases foci of infection were removed either a few days prior or subsequent to the injection; this probably was an occasional factor in the cure. Table 2 gives the relation of eradication of the foci to the results; the data are of interest, but definite conclusions cannot be drawn from them.

TABLE 2
RELATION OF ERADICATION OF FOCI TO RESULTS

Patients with permanent relief.....	9
Foci of infection removed in.....	5
Patients with partial permanent relief.....	14
Foci of infection removed in.....	11
Patients without permanent benefit.....	11
Foci of infection removed in.....	5
Patients in whom foci were removed.....	21

While our results are not entirely satisfactory and as yet we do not know what part the injection plays and what part the removal of foci plays in bringing about the beneficial effect, we believe that the procedure is justified in selected cases of sciatica.

SUMMARY

In thirty-four cases of sciatica in which a definite removable cause could not be found, the removal of possible foci of infection in 62 per cent combined with repeated epidural injections gave a permanent cure in 27 per cent, and permanent amelioration of symptoms in 40 per cent, so that the patients were able to continue their occupation with a fair degree of comfort. Thirty-three per cent did not obtain permanent beneficial results.

TECHNIC

A TECHNIC OF INTRAMUSCULAR (EPIFASCIAL) INJECTION*

JOHN H. STOKES

So-called intramuscular injection is a procedure technical acquaintance with which is generally taken for granted in therapeutic instructions, so that a rehearsal of the steps of the procedure seems correspondingly uncalled for. Observations extending over several years have led me to suspect, however, that this method of administering medication in general, and mercurial preparations in particular, involves certain principles and a degree of manual dexterity for its accomplishment *secundum artem* with which physicians are often unfamiliar. A folder recently issued by a pharmaceutical concern, purporting to describe a satisfactory technic for the intramuscular injection of one of its preparations, seems, at least so far as its illustrations go, to violate the first principles of intramuscular technic. For these reasons the following description of a mode of procedure which has proved serviceable in about 40,000 injections is offered.

My experience with the injection of large quantities of solutions (100 c.c. or more) into the buttocks directed my attention to a phenomenon which suggested that the contents of the so-called intramuscular injection when properly introduced are deposited not within the body of the gluteus maximus or between its fasciculæ, nor yet within the subcutaneous fat, but in the areolar tissue on the upper surface of the fascia forming the extension of the fascia lata covering the gluteus maximus. A large quantity of fluid when thus injected instead of forming a tense induration in the body of the muscle or spreading laterally on to the hip and thigh or appearing at the sacral margin presents promptly at the lower border of the buttock in the gluteal sulcus. The markedly better absorption thus obtained and the freedom from local irritation even on the injection of a highly irritating drug were demonstrated by the work of Wechselsmann and Eicke,† who advocated this

* Reprinted from the Medical Record, 1921, xcix, 730-734.

† Wechselsmann and Eicke: Zur Technik und Wirkung subkutaner Neosalvarsaninjektionen. München. med. Wchnschr., 1914, lxi, 535-538.

technic for the comparatively painless and uncomplicated administration of arsphenamin intramuscularly. A similar principle may be employed in the administration of the mercurial preparations into the tissue of the buttock with equally satisfactory results. The technical detail necessary to achieve this end, and the avoidance of other familiar complications of intramuscular injection, such as deep and superficial infiltrations, embolism, necrosis, and abscess formation, may be briefly described as follows:

1. *The position of the patient.*—Injections into the buttock are given to best advantage with the patient lying prone on a table. Other positions induce tenseness of the tissues, which favors leakage of the injected substance along the needle track, makes a careful estimation

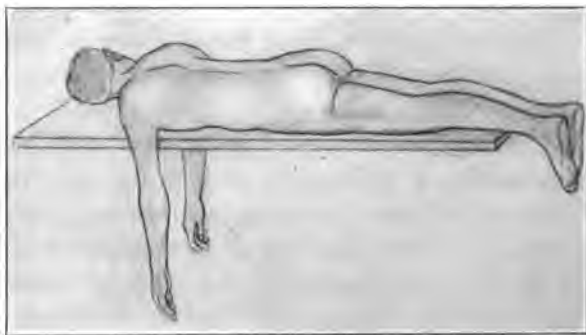


FIG. 316.—Prone position for intramuscular injection, showing arms hanging over the sides of the table to promote relaxation.

of the depth of tissue and the placing of the needle difficult, and also makes it difficult to avoid mechanical awkwardness in carrying out the procedure.

Relaxation after the patient assumes the prone position should be complete. Attention to certain details assists in securing a satisfactory coöperation on this point. The patient should drop his arms over the side of the table (Fig. 316). His legs should be placed in a position of moderate internal rotation "toed in" (Fig. 317 (a)). The difference in the appearance of the buttock when the patient attempts to keep the heels together is well shown in Figure 317. Dimpling of the lower outer quadrant of the buttock as shown in (b) disturbs the anatomic relations, is a sign of incomplete relaxation, and is the position ordinarily assumed by every patient who fears the introduction of the needle.

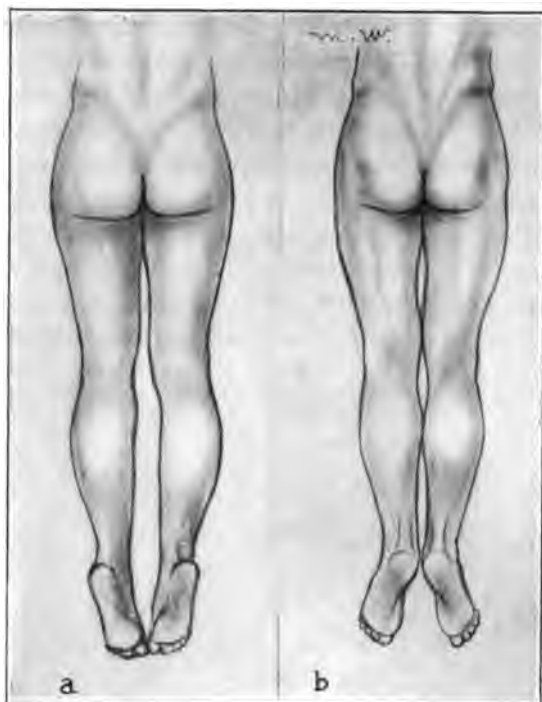


FIG. 317.—a, “Toed in” to show the relaxation of the buttock. b, “Toed out” with the dimpling of the buttock indicative of a tense musculature.

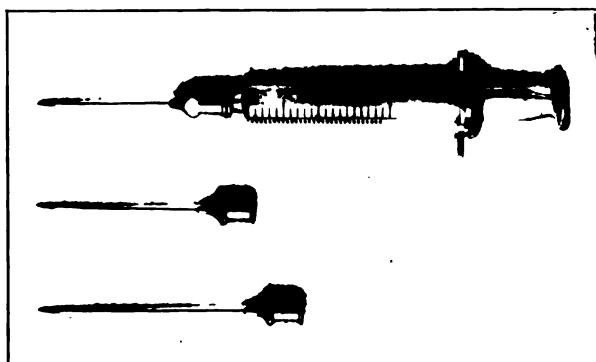


FIG. 318.—All glass Luer syringe with the various sizes of needles used for intramuscular injection.

2. *Instruments.*—The 2 c.c. glass Luer syringe and three lengths of needles, one for very thin or flabby buttocks, one for medium, and one

for fat buttocks, are necessary. The aspiration technic described herewith for detecting the presence of a needle in a vein makes possible the use of a smaller gauge needle than that required when the venous pressure alone is depended on to yield a flow of blood from a misplaced needle. My preference is for 22 gauge needles 1.5 inches, 2 inches, and 2.5 inches from the tip of the hub to the point (Fig. 318).

3. *Point of injection.*—Injections into the buttock should, in general, be given into the upper outer quadrant near its inner angle, approximately at the point indicated by a dot in Figure 319. If the injection is given into the upper part of the outer quadrant or into the inner

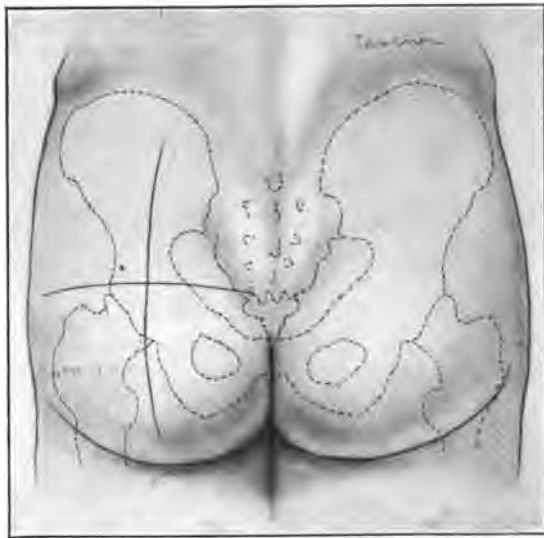


FIG. 319.—Outline of the buttock and pelvic bones illustrating (black dot) the point in the upper outer quadrant about which injections may be made to the best advantage.

quadrant near the sacrum, even a short needle is likely to strike bone, or the injection of the irritant substance above the periosteum or about the roots of the sacral plexus will give rise to induration and pain, and may, as Neisser points out, induce an obstinate sciatica. Injections given into either of the lower quadrants are subject to pressure on sitting, and are correspondingly painful. If administered near the great sciatic nerve a neuritis may result. Such injections, moreover, cannot be deposited on the fascia with the exactitude possible in the upper outer quadrant, and for this reason are likely to give rise either to superficial nodule formation, abscesses, or deep firm indurations.

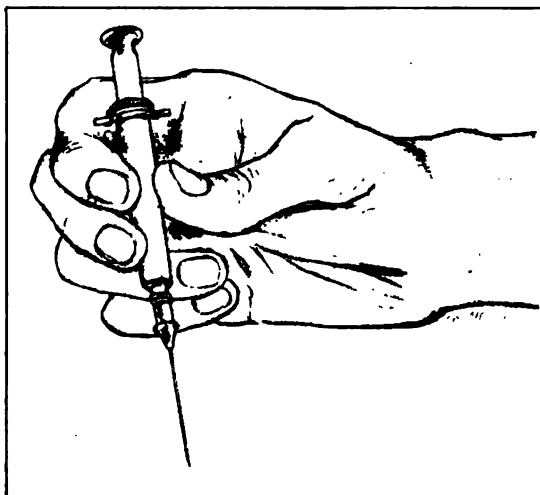


FIG. 320.—Right hand holding the syringe.

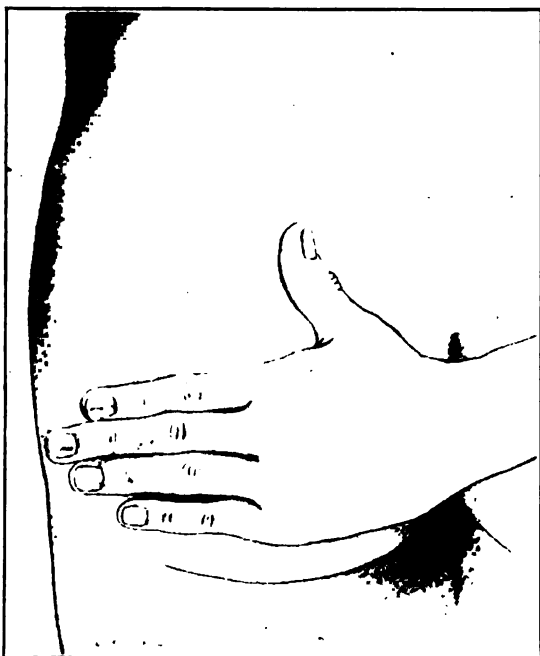


FIG. 321.—Left hand drawing down the buttock.

4. *Technic of injection.*—The syringe and needle may be sterilized with alcohol. The alcohol should be thoroughly expelled from the

syringe and the needle wiped with sterile cotton moistened with alcohol. The emulsion is then aspirated into the syringe through the needle which has been previously attached, and the needle is again wiped. The syringe is grasped in the right hand (Fig. 320). The left hand is placed flat on the buttock and with moderate pressure is drawn firmly downward toward the patient's heel, thus flattening and fixing the tissues (Fig. 321). The syringe is introduced to its full length by a quick stroke at an angle of approximately twenty degrees from the



FIG. 322.—Introduction of the syringe.

vertical in a sagittal plane, with a slight inclination inward (Fig. 322). The removal of the left hand slightly increases the slant of the syringe. During the process of introducing the needle the piston must be controlled by the pressure of the index finger against it above the barrel, to prevent the leaking of a solution or thin emulsion.

5. *Testing for the presence of the needle in a blood vessel.*—As soon as the needle is introduced the syringe is steadied with the left hand while an attempt is made to aspirate by pulling upward on the piston with the right hand (Fig. 323). This attempt should be continued for at

least ten seconds. This in my experience is an entirely safe and much more trustworthy method of detecting puncture of a deep vein or capillary than is the mere detaching of the syringe or the introduction of an empty needle in the expectation that the pressure of the blood in a capillary vessel will cause a backflow of emulsion or of blood, as the case may be. I have never seen an accident of any type occur if the aspiration step in the technic was rigidly adhered to. As soon as it appears that nothing can be aspirated from the deep tissue about the



FIG. 323.—Aspiration to test for the presence of the needle in a vein.

needle point, the contents of the syringe may be injected (Fig. 324), the right hand maintaining the proper angle of the needle.

It is not necessary in this technic to use a sign, such as Wechselmann's torsion sign, for demonstrating that the needle point is near or on the fascia. The site of the injection, the length of the needle when properly adapted to the type of buttock, the fixation of the tissue with the left hand, and the position of the syringe when introduced soon become matters of habit and seem to place the injected material in

such a way that induration is a very unusual occurrence. The flow of injected material into the tissue should be free and the needle point should not "feel" as if stuck in a board. A little experience soon enables one to control the technic by recognizing the deep, painful induration 4.5 to 7 cm. in diameter that has followed on too deep injection (intramuscular) and nodules 1 to 2 cm. in diameter in the skin or panniculus secondary to too superficial injection or to leakage along the needle track.



FIG. 324.—Injection. The emulsion or solution should flow in freely and not have to be forced.

Deposition of injected material along the needle track is avoided: first, by securing complete relaxation; second, by using a small caliber needle; third, by completely emptying the syringe before withdrawal; fourth, by a rapid withdrawal; fifth, by quickly pushing the tissues which have been drawn downward by the left hand back to their normal position like a sliding valve the moment the needle is withdrawn; and sixth, by light massage with a cotton pledget over the site of puncture which results in a rapid flattening out of the injection mass

in the areolar tissues over the fascia (Fig. 325). In buttocks which have been rendered fibrous by repeated courses of intramuscular injections, leakage cannot be prevented, and the intramuscular injections must ultimately be abandoned.

Attention to several additional details materially contributes to a uniformly satisfactory technic. It goes without saying that the buttocks should be used in alternation for injection. Needle points should



FIG. 325.—On release of the left hand the tissues of the buttock return to their normal position, producing a valve action. The emulsion is spread out in the epifascial tissue and leakage prevented by massage with a cotton pledget.

be of a rather long bevel and exceedingly sharp. The use of a needle with a turned point is very painful. In wiping the needle a turned point can be detected by a grating sound and feel as it passes over the cotton, often when it is scarcely visible. The operator may unconsciously turn the point of his needle by touching it against the bottom of his bottle of emulsion or solution when filling the syringe. For this reason every movement of the needle should be carefully controlled and it should never be brought into contact with hard substances. A needle which

has been allowed to become rusty, corroded, or pitted will also bring a protest from the patient.

The breaking of a needle is one of the most unpleasant complications of intramuscular injection and may be due first, to an incorrectly placed puncture which causes the needle to strike on bone, fracturing it at some point along the shaft; second, to a sudden movement on the part of the patient, especially if the point is caught in the fascia or lies in the muscle, and third, to weakening of the needle by internal or external corrosion. The first cause seldom operates except as a result of gross misjudgment. The second can usually be avoided by an effort to secure the cooperation of the patient and by guarding against sudden movement in those in whom cooperation cannot be expected (children for example). The third cause can be controlled by frequent inspection of needles with a forcible attempt to bend the shaft on the hub. If a steel needle is used for corrosive solutions its life will be comparatively short and inspection must be frequent and critical.

If a needle breaks.—First, do not exclaim or discuss the situation with the patient or the nurse; second, keep the left hand in position until an attempt can be made to recover the needle. The usual point of fracture is at the juncture of the hub and shaft and with an assistant at hand the fragment just beneath the skin may sometimes be recovered by a small incision and with the aid of a hemostat, if the operator keeps his presence of mind. On the other hand, the moment the left hand is released from the buttock the needle is lost and can usually only be identified by the roentgen ray and removed through an extensive surgical incision. Such situations are so embarrassing that the finest types of steel and tempered gold needles should be used for intramuscular work.

In the use of insoluble suspensions for intramuscular injection a word of caution as to the preparation of the suspension is important. Concentrated suspensions requiring small amounts for each injection are often less painful than thin suspensions. An insoluble preparation made up in a fluid base settles rapidly and the collected powder can only be returned to suspension by from five to twenty minutes persistent vigorous shaking and kept in suspension by shaking after each injection. The suspension may appear entirely homogeneous when a considerable portion of the solid material still adheres to the bottom of the bottle. A satisfactory test of complete suspension consists of shaking until none of the suspension can be recognized in the groove at the juncture of the sides and bottom of the bottle when the bottle is inverted.

6. *Treatment of complications.*—If blood is obtained on aspiration after the introduction of the syringe, even in the minutest amount, the syringe should be withdrawn and the procedure repeated 1 cm. or more from the site of the unsuccessful attempt. To continue the injection in the face of a return of blood or even a tinged suspension may be attended by fatal consequences from embolism.

Superficial indurations or nodules may be treated by painting them once or twice a week with iodine and requesting the patient to pinch and massage them between the thumb and forefinger. Deep indurations attended with pain from injection below the fascia are much relieved by prolonged hot applications and massage. Indurations seem to occur with special frequency in certain subjects, especially the obese, and are sometimes unavoidable even with the best technic. Each node represents a certain amount of encapsulated mercury which may be abruptly released for absorption by trifling trauma such as that of sitting down more heavily than usually. The sudden onset of salivation in patients who have not had intramuscular injections of insoluble mercurial salts for a considerable period may be to some extent a result of technical errors which have interfered with absorption. There can be no object in continuing a method of administration in which persistent nodule formation even with a careful technic shows that the drug does not absorb.

Pain referred down the leg has always in my experience been evidence of the technical error of injecting too deep or too near the sacral plexus and the great sciatic nerve.

Pulmonary embolism following the use of insoluble salts, such as mercury salicylate, calomel, and gray oil, probably cannot be absolutely avoided, but should be an excessively rare occurrence. The symptoms of pulmonary embolism may vary from a slight and transient cough after the patient rises from the table to evidences of extensive pulmonary infarction with severe and persistent cough, rise of temperature, pleural irritation, and occasional pneumonic complications. Pulmonary embolism may occasionally supervene some hours after an injection made in accordance with the strictest technical exactness. Cerebral embolism is exceedingly rare.

Abscess formation I have seen only twice in 40,000 injections. The abscess is usually sterile and resolves promptly on evacuation. A certain percentage of deep indurations doubtless undergo central softening, but under rest and hot dressings the process subsides.

THE SURGICAL REMOVAL OF PANCREATIC STONES

A REPORT OF FOUR CASES *

WALTER E. SISTRUNK

Pancreatic stones occur so infrequently that surgeons are seldom called on to remove them. Very few cases have been reported in the literature in which a pancreolithotomy has been performed. It is probable that the stones are occasionally overlooked during abdominal explorations, as they have been found a number of times at necropsy. The consistency of the pancreas is probably responsible for the difficulty with which the stones are recognized at operation; when they are multiple a sense of crepitation is brought out on palpating the gland, which makes the diagnosis easy, but it is difficult to recognize single stones by palpation through the pancreatic tissue.

In a review of the histories of the patients operated on for pancreatic stones in the Mayo Clinic, I find that during the eleven years since 1910 this operation has been performed only four times. It is customary in the Clinic routinely to examine the pancreas in all patients operated on for upper abdominal disease, and the fact that so few pancreatic calculi have been found by experienced surgeons during this time shows that pancreatic calculi are either extremely rare or very difficult to recognize at operation.

The presence of stones in the pancreas was first reported by Graaf, in 1667, and the first report of the surgical removal of stones was probably that of Gould, in 1896. Since then reports of cases have occasionally been published, but the list is extremely small.

Pancreatic stones very closely resemble the calculi found in the ducts of the salivary glands. Usually they are white or slightly gray, firm in consistency, and irregular in shape; however, they may be faceted on a portion of their surface, as were the stones removed from one of the patients in the Clinic. Chemical analyses show that they are com-

* Presented before the American Surgical Association, Toronto, June 15, 1921. Reprinted from *Annals of Surgery*, 1921, lxxiv, 380-389.

posed of carbon salts, phosphorus, or magnesium salts, and organic matter.

As there is still considerable controversy with regard to the etiology of pancreatic diseases it is difficult to know just how these stones are formed and the part they may play in pancreatic disease. It would seem, however, that the manner of their formation must be similar to that of stones in the biliary tract, that is, from infection in the ducts, or from the stagnation of pancreatic fluids from obstruction.

Diabetes has been observed often with pancreatic stone. Hanse-mann, in seventy-two cases of diabetes associated with pancreatic disturbances, found stones in twelve, and Oser in seventy cases of lithiasis observed that diabetes was recorded in twenty-four. It is difficult to determine just what part, if any, these stones played in the production of the diabetes. It is probable that the diabetes and the stones resulted from the chronic inflammatory changes in the pancreas, but it is possible that the diabetes may have resulted from the chronic inflammatory changes produced in the gland by the calculi.

When the pancreatic ducts enter separately into the duodenum it seems quite likely that the formation of stone in only one of the ducts would not necessarily produce marked disturbance, as experimental surgery has shown that new ducts form readily following ligation of one of the main ducts. Pancreatic stones have been reported in some cases of pancreatic cysts, and it is probable that they are responsible for the formation of certain of these cysts.

The symptoms produced by stones in the pancreas are so similar to those of chronic pancreatitis associated with stones in the biliary tract that a definite diagnosis of their presence in the pancreatic ducts is impossible. The presence of stone may be suspected, and several cases have been reported in which such a diagnosis was made and was later confirmed at operation, but a definite diagnosis can be made only at operation. On account of this difficulty in diagnosis the pancreas, during the course of operations for infection or stones in the biliary tract, should be carefully palpated for evidences of stone.

Pancreatic stones may be single or multiple; they may entirely fill both pancreatic ducts. They also have been found near the periphery of the gland where they formed in the small ducts. When they are in the ducts near the point where the ducts empty into the duodenum they may often be recognized at operation by careful palpation; if multiple, they may be recognized by the peculiar feeling of crepitation

which they impart to the palpating hand on manipulation of the gland. It is difficult to decide definitely with regard to the character of localized tumors in the head of the pancreas, as these may be due either to neoplasms or to impacted stones surrounded by an area of inflammation. In one of the patients operated on in the Clinic, as in a case reported by Link, there was a distinct ridge on the anterior surface of the gland corresponding to the course of Wirsung's duct, which could be felt throughout the entire length of the pancreas.

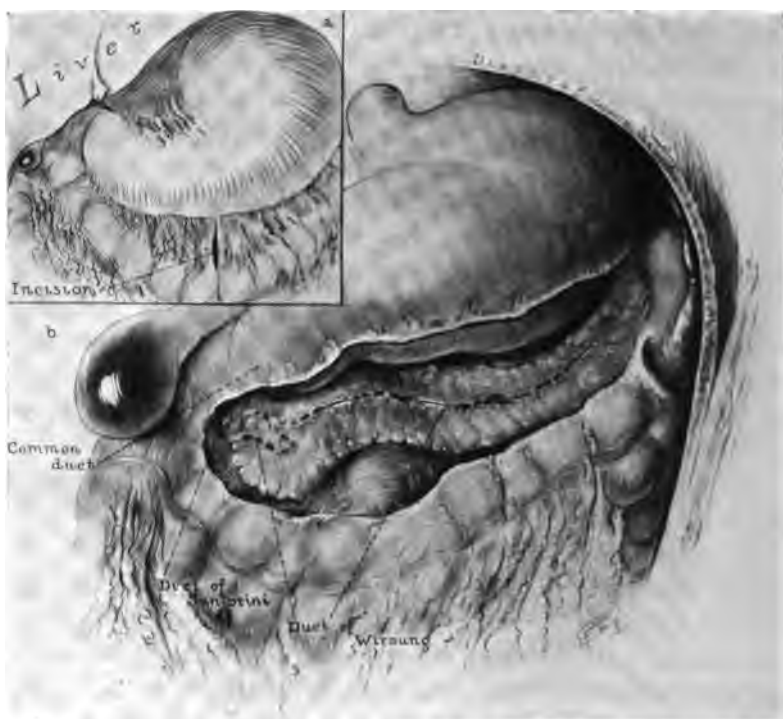


FIG. 326.—a, Incision in the gastrocolic omentum. b, Opening in the lesser peritoneal cavity and incisions along the course of the pancreatic duct. The gastrocolic omentum has been divided extensively in order to show the entire pancreas.

Very few operations have been performed on the pancreas itself, and in most instances the chronic inflammatory diseases of the gland have been treated indirectly by drainage of the gallbladder or common duct. Experimental work by Opie, Coffey, Sweet, and others tends to show that surgery of the pancreas is not necessarily attended with the risk commonly attributed to it.

Operations for the removal of pancreatic stones present no unusual difficulties except in instances in which the stones are impacted in the ducts near the ampulla, and I believe they usually can be performed safely. The pancreas should be exposed by the route which seems to offer the best exposure. If the stomach is high the gland is best exposed through the gastrocolic omentum (Figs. 326 and 327); if the stomach is

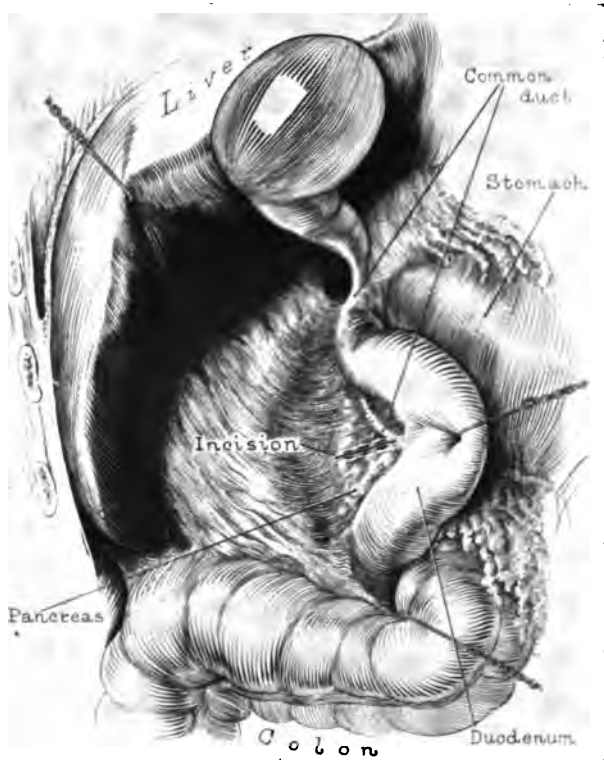


FIG. 327.—The mesentery of the duodenum is incised and the duodenum turned back in order to expose the head of the pancreas.

low, it is best exposed through an opening in the gastrohepatic omentum. The pancreas may also be exposed by lifting up the omentum and colon and making an incision through the transverse mesocolon; or stones may be removed from the lower portion of the duct of Wirsung through an incision through the mesentery of the duodenum; cases have been reported in which the anterior wall of the duodenum has been opened and stones removed by incising the papilla of Vater and the

posterior wall of the duodenum, thus exposing the ampulla and the end of the pancreatic duct. Following the removal of stones hemorrhage may be controlled and the opening in the duct closed without difficulty with small silk sutures. In the case reported by Link the tail of the pancreas was drawn out through an opening made in the transverse mesocolon, and, after the stones had been removed, a catheter was used to drain the pancreas, the tail of which was drawn out through the abdominal incision.

The ducts of the pancreas are without valves, and in cases of obstruction in which pancreatic drainage seems advisable it is possible that an operation of the type described by Link, or that described by Coffey, in which the cut-off end of the pancreas is transplanted into the jejunum, might be performed. In the four cases in the Mayo Clinic the openings in the pancreatic duct were closed and rubber tissue drains used to take care of any pancreatic fluids which might escape. The experimental work of Opie, which has been confirmed by Coffey and others, has shown that fat necrosis occurs only when pancreatic fluid is poured into and confined in the retroperitoneal fat; when pancreatic fluid is delivered inside the unbroken peritoneum fat necrosis does not occur, and no harm can result provided sufficient drainage is placed to conduct the pancreatic fluid to the surface. It would seem safest, therefore, in operations in which the pancreatic ducts are opened that some provision be made for carrying off the pancreatic fluid in case leakage should occur.

REPORT OF CASES

Case 1 (A38678). Mrs. J. F. K., aged forty-eight years, registered at the Clinic June 9, 1910. She had had attacks of sudden, sharp, cramp-like pains in the epigastrium for fourteen years. The pain radiated to the back, was accompanied by nausea, and often by deep jaundice. For many years she had had a great deal of flatus and diarrhea, without blood or mucus, often having as many as twenty-five stools in twenty-four hours. She had had jaundice for one year and had lost weight and strength.

A diagnosis of gallbladder disease with probable common duct stones was made.

Operation was performed June 16, 1910. One stone 1 by 2 cm. and several smaller ones were removed through an incision in the anterior wall of the duodenum; the larger stone was found about 1.2 cm. above the papilla. The ampulla was opened for a distance of about 1.8 cm. The gallbladder was largely destroyed and remnants of it were removed. The spleen was four times normal size. The patient also had pyloric obstruction from chronic duodenal ulcer and a gastro-enterostomy was made later. Two years afterward the patient was in excellent health.

Case 2 (A288735). Mr. C. V. M., aged thirty-three years, who was examined in the Clinic September 11, 1919, gave a history typical of gallstones for several years. One year before he had been operated on elsewhere and stones from the gallbladder and com-

mon duct were removed and the gallbladder drained. The pancreas was found to be enlarged and appeared to contain stones, but no attempt was made to remove them.

Examination of the patient revealed diabetes. Sugar disappeared from the urine under treatment and strict diet.

Operation was performed October 1, 1919. The gallbladder was enlarged, but free from stones. Two stones were removed from the common duct. The pancreas was slightly enlarged and quite hard. A peculiar crepitating feel was imparted to the hand on palpating the pancreas, and a ridge could be felt on the anterior surface of the gland corresponding to the course of the duct of Wirsung, which extended from the tail to the head. The pancreas was exposed through the opening in the gastrocolic omentum and many stones were removed through four incisions in the duct of Wirsung (Fig. 328). Several stones in the duct near the ampulla were removed through an opening made



FIG. 328 (Case A288735).—Pancreatic stones.

through the mesentery of the duodenum. The openings in the duct were closed with small silk sutures. The gallbladder and common duct were drained by several rubber tissue drains. The duct of Santorini seemed to be filled with stones, but on account of the extent of the operation already performed no effort was made to remove them. The diabetic condition improved considerably after operation and sugar tolerance became much increased. Recently the patient has had symptoms indicating that infection is still present in the biliary tract.

Case 3 (A309528). Mrs. C. P., aged sixty-eight years, was examined March 3, 1920. She had had attacks of epigastric pain radiating to the left side, but not to the back for a number of years. She had lost 15 pounds in weight within the last year.

The appendix was found to be definitely diseased. Multiple stones could be palpated in the head of the pancreas.

The stones were removed through an opening through the mesentery of the duodenum. The stones appeared to be in the main duct of the pancreas, but they were near the surface. The patient recovered uneventfully.

Case 4 (A345511). Mrs. J. J. R., aged sixty-two years, came for examination January 7, 1921. She gave a history of ulcer of the duodenum of fifteen years' duration.

Examination did not disclose evidence of gallbladder trouble. The roentgenograms revealed pyloric obstruction.

Operation was performed January 13, 1921. A chronic perforating duodenal ulcer with pyloric obstruction was found. A stone could be palpated in the pancreatic duct near the ampulla. An opening was made in the duct through the mesentery of the duodenum and two stones 0.5 by 0.5 by 1 cm. were removed. A gastro-enterostomy was made. The patient made a good recovery.

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AUTOGENOUS BONE TRANSPLANTATION*

MELVIN S. HENDERSON

Before beginning my address I wish to thank you for the honor and distinction you have conferred on me in making me the chairman of this section. My pleasure in acting in this capacity is made greater by the presence of our distinguished visitors from abroad, Sir Robert Jones of England, Doctor Jacques Calve of France, and Signor Putti of Italy. Their names are household words in our orthopedic world. I take this opportunity to extend to them the appreciation of their presence by the members of this section and assure them of the very great pleasure and profit we have derived from their writings and teachings, and shall derive at this meeting through their addresses and discussions.

In my discussion I shall attempt to place briefly before you my experience in autogenous bone transplantations. I have carefully reviewed, with the assistance of Dr. Pio Blanco, the records in the Mayo Clinic, of 418 patients on whom bone transplantation had been performed during the eight years between January 1, 1913 and January 1, 1921. It would be confusing and tiresome to discuss in statistics alone, so I trust you will pardon me if my deductions at times seem to be dogmatic. As nearly as possible I have based deductions on accurate clinical information, not trusting merely to clinical impressions. It is my hope that the conclusions and the deductions reached from this experience and study will be of interest and possibly some value to you. There is no need to review the literature, for that has been done thoroughly by others. I feel, however, that I should express my appreciation of the impetus given this subject by Dr. F. H. Albee and the late Dr. J. B. Murphy.

The study of autogenous bone transplantation is so interesting that it is difficult to adhere closely to the subject and not to follow out the

* Chairman's Address, presented before the Section on Orthopedic Surgery at the Seventy-second Annual Session of the American Medical Association, Boston, June, 1921. Reprinted from the Journal of the American Medical Association, 1921, lxxvii, 165-168.

many leads suggested by the investigation, but I shall try to keep to the main facts.

One hundred sixty-six of the 413 patients were suffering from tuberculosis of the spine and were subjected to the operation, with various slight modifications, as originated and advocated by Albee. Of the remaining 247 patients all but a few were operated on for ununited fractures.

SPINAL TRANSPLANTS

The definite end results of spinal transplantation are not easily determined. Contrary to conditions in the fracture group we are dealing with a condition which though it may be the disabling factor, is practically always a secondary manifestation of a focus elsewhere. The operation and subsequent mechanical treatment are only a part of the procedure. Therefore conclusions in such a group are more or less unreliable. It is not possible to see all the patients, one, two, or more years after operation and many times inferences must be drawn from correspondence.

The data I have to offer with regard to end results are based on 132 patients who could be traced out of a total of 141 patients operated on more than eighteen months before. I have classified the disease as arrested or cured when the patients were free from pain and were able to resume their occupations, although not necessarily their original occupations. The postoperative complications of the entire group of 166 is available for study. There were only nine children in the series, since the operation is rarely advised for them.

Of the 132 patients concerning whom we were able to learn enough to warrant an opinion with regard to the end results there were sixty-six (50 per cent) who may be considered cured, or with the disease arrested. Twenty-nine (21.99 per cent) were improved, twenty-two (16.66 per cent) were unimproved, and twelve (9.09 per cent) died later. The exact cause of death in all instances could not be determined, but from correspondence with the patients' relatives and physicians I should judge that the majority died of disseminated tuberculosis. Three (2.26 per cent) died so soon after operation that their deaths must be regarded as postoperative mortalities; one dying of pulmonary embolism on the fourteenth day and two of tuberculous meningitis in about the fourth week.

Only four (2.4 per cent) of the 166 patients had postoperative infec-

tions, which is remarkable since all of the patients had had two incisions, one in the back and one in the leg. The legs were not infected, but in a few instances a hematoma developed which discharged bloody fluid and then healed. In at least two of the four patients who became infected, I believe the cause was the breaking through into the wound of a tuberculous abscess. The graft was lost in two patients. In a

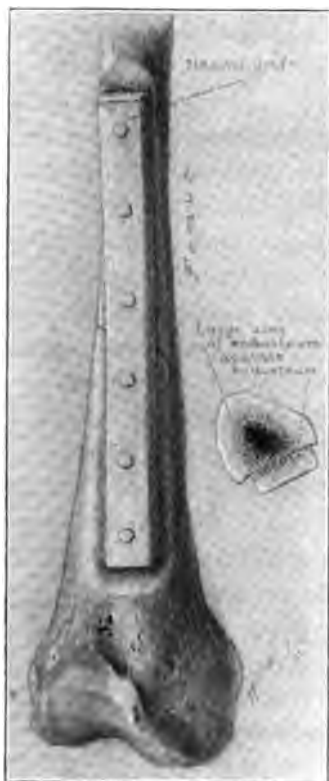


FIG. 329.—Massive autogenous graft applied to femur and held in place by six beef-bone screws. This graft gives abundant contact of endosteum to endosteum.

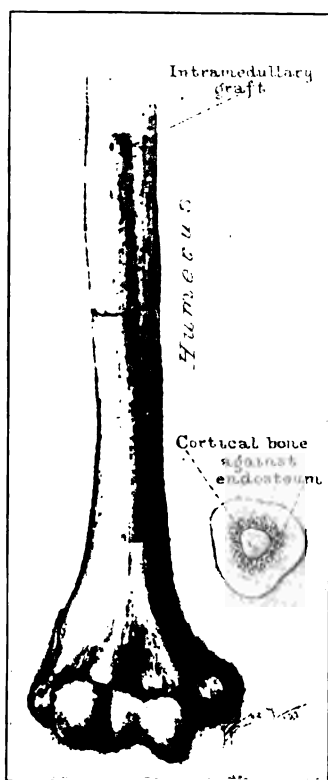


FIG. 330.—Intramedullary autogenous graft. No contact of endosteum to endosteum. In this situation the graft is a foreign body and will be absorbed.

few patients the devitalized skin over a prominent kyphos broke down; the exposure of the graft to the air caused a localized osteomyelitis. In two patients we later chiseled off the dead portion of the graft, which was followed by healing of the ulcer. This condition cannot rightfully be called an infection. In four patients who were not doing well the roentgenograms disclosed the graft fractured over the kyphos,

and in two we placed a graft on the opposite side of the spinous processes. In a few cases we showed poor judgment in advising operation, failing to appreciate the poor condition of the patient. Generally speaking, draining sinuses, no matter where they are situated, and pulmonary tuberculosis, unless quiescent, contraindicate surgery. A few

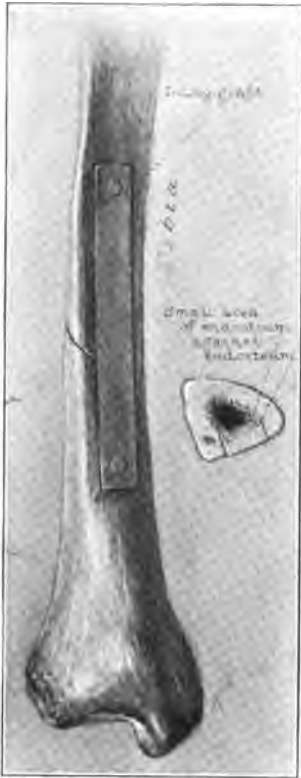


FIG. 331.—Inlay autogenous graft applied to the tibia. Contact of endosteum to endosteum over a limited area. Two beef-bone screws are used to steady the graft.

of the grafts became loose and one end protruded against the skin because they were put in under tension. A bone graft should never be under tension. By taking the bone from the flat internal surface of the tibia the graft can be sufficiently curved to fit almost any kyphos. I have found it advantageous to hold the transplant against the denuded spinous processes with beef-bone screws using 6-32 machine size screws carefully placed at some distance from the kyphos, for a screw hole through the transplant at the apex of the kyphos might lead to fracture of the graft. This procedure is not always possible, particularly when the site of operation is in the upper dorsal region, the structure and slant of the spinous processes making it difficult to place the screws (Table 1).

The operation is in no sense of the word radical and the patient cannot be offered the advantage of a removal of a portion of the tuberculous tissue and débris, as is offered in a resection of the knee. It would be an interesting contribution to our knowledge if two groups of patients of like age and under the same surgical control could be studied, one group being operated on, the other not operated on, and all the patients confined to bed for equal periods and the same suspension. I have not, however, made such a study and can merely state

TABLE 1
SPINAL AUTOGENOUS BONE TRANSPLANTS

Patients operated on previous to January 1, 1921.....	166
Patients operated on previous to January 1, 1920.....	141
Patients operated on previous to January 1, 1920, traced.....	132
Cured (or disease arrested).....	66 (50 per cent)
Improved.....	29 (21.9 per cent)
Unimproved.....	22 (16.66 per cent)
Operative deaths.....	3 (2.26 per cent)
Later deaths.....	12 (9.09 per cent)

One hundred sixty-six patients each with two large incisions gave four (2.4 per cent) infections. The graft was lost in two patients. Prominent kyphos may cause ulcer. Four patients fractured the graft and two were reoperated on. Occasional loosening of one end of the graft occurred due to tension. A curved graft and beef bone screws should be used.

that my opinion concerning this group of patients who are subjected to bone transplantation for tuberculosis of the spine is that the results are more favorable than in those not operated on; that owing to the uncertainty of the fate of the bone graft in children I seldom advise the operation for them, and finally, that as the theory of the operation is logical and it gives better control of the average patient, I shall continue to advise the operation in adults.

TRANSPLANTS FOR DELAYED UNION, NONUNION, AND OTHER CONDITIONS

Two hundred forty-seven patients were operated on for ununited fractures, bony defects, and so forth, and in all fairness, I may say that as a group they are difficult to treat successfully. One hundred thirty-nine of the 247 had been operated on elsewhere, from one to six attempts having been made to induce union. Fifty-nine had been infected; many had great masses of scar tissue and the skin was adherent to the bone, so that a slough would have followed any interference. In some the mistake was made of operative inference too soon after the cessation of discharge, and the infection was stirred up again.

TRANSPLANTS FOR UNUNITED FRACTURES OF THE LONG BONES

Patients with fracture of the tibia (102) formed the largest group. Fifty-five of these had been operated on elsewhere. Two patients (1.9 per cent) died from influenza. There were four (5.4 per cent) infections in seventy-three clean cases, but the graft was not lost. There were nine (31 per cent) infections in twenty-nine cases that were

clean at the time of operation, but had been infected previously. The bone graft was lost in four patients of this group. Seven patients were not traced. Thus there are ninety-five patients on whom to base our statistics of the end results.

Eighty-five operations (89.4 per cent) were successful; eight (8.8 per cent) were failures. In order to secure the eighty-five cures six patients were operated on twice; in other words, 101 operations were performed on the ninety-five patients.

In thirty-six patients, ten having been operated on elsewhere, bone transplantation was performed for ununited fractures of the femur. There was one operative death (2.07 per cent). In thirty-four clean cases there were three (8.8 per cent) infections; one graft was lost. Two cases clean at the time of operation, but having been infected previously, suppurated and one graft was lost. Three patients were not traced; this leaves thirty-three patients on whom to base statistics of the end results. Nineteen of these (57.5 per cent) were cured and thirteen (39.3 per cent) were not cured. Three of the patients were operated on more than once, making thirty-six operations on thirty-three patients, and, basing the statistics on the number of operations, 52.7 per cent were cures. Twenty of the transplants were performed for old ununited fractures of the neck of the femur, with eleven successes and nine failures. Twelve were performed on the shaft, with eight successes and four failures.

Bone was transplanted to the radius in thirty-five patients, twenty-three having been operated on elsewhere, but as seven (20 per cent) were not traced, we were able to ascertain the end results in only twenty-eight patients; the statistics are compiled from these. Twenty-two (78.5 per cent) of the operations were successful; six (21.5 per cent) were failures. One patient was operated on by us twice. In twenty-eight clean cases not infected previously there were five (17.9 per cent) infections and two grafts were lost. Three (42.8 per cent) of the seven cases previously infected suppurated, but only one graft was lost.

The humerus was operated on in thirty-four patients, and all but one were traced. Twenty-six of these patients had been operated on elsewhere, some of them three and four times. Twenty-seven of the operations were performed in clean fields without infection previously and four (14 per cent) became infected, but only one bone graft was lost. Seven cases were clean at the time of operation, but had been infected previously. Four (57 per cent) became infected and four bone

grafts were lost. There were twenty-three (69.6 per cent) successes and ten (30.03 per cent) failures. One patient was not traced. Six patients were operated on more than once, making thirty-nine operations on thirty-three patients with twenty-three successes (56.4 per cent).

Transplantations to the ulna were performed in eighteen patients. Seventeen of the cases were clean and had not been infected previously, but two (11.7 per cent) became infected and in one the graft was lost. One infection developed in a patient who had been infected previously, but the graft was not lost. Two of the patients in this series were not traced, thus leaving sixteen for purposes of estimating end results. Thirteen (81.2 per cent) of the operations were successful, three (18.7 per cent) were failures.

Autogenous grafts were used in nine patients who came to the Clinic with nonunion following resection of the knee. Only six of these could be traced, all (100 per cent) had union. One patient was infected and lost sight of. A bone graft was used in the patella in two instances; one patient could not be traced; the other obtained a good result. A graft was used in the nose once and in the sacro-iliac joint once. Nine patients with ununited fractures of the jaw were operated on. All were traced and in seven (77.7 per cent) union resulted. One became infected, but the wound healed later, and one died of an intercurrent affection (Tables 2 and 3).

TABLE 2
AUTOGENOUS BONE TRANSPLANTS FOR UNUNITED FRACTURES

	Traced.	Operations.	Success.	Failure.	Death.
Tibia	95	101	85	8	2
Femur	33	36	19	13	1
Radius	28	...	22	6	
Humerus	33	39	23	10	
Ulna	16	...	13	3	
Ununited knees	6	...	6		
Jaw	9	...	7	1	1
Patella	1	...	1		
Nose	1	...	1		
Sacro-iliac	1	...	...	1	
Total	223	176	177	42	4

There were 247 cases in all, but only 223 were traced, with 177 (79.3 per cent) successes and forty-two (18.8 per cent) failures. There were four (1.7 per cent) deaths, three due to influenza; one due to a cerebral embolus in a femur case. Tibia, 101 operations on ninety-five patients, giving 84.1 per cent successes. Femur, thirty-six operations on thirty-three patients, 52.7 per cent successes. Humerus, thirty-nine operations on thirty-three patients, 56.4 per cent successes.

TABLE 3
AUTOGENOUS BONE TRANSPLANTS FOR UNUNITED FRACTURES

	Clean cases.	Infected.	Previously infected.	Infected.	Graft lost.
Tibia.....	73	4 (5.4 per cent)	29	9 (31 per cent)	4
Femur.....	34	3 (8.8 per cent)	2	2 (100 per cent)	2
Radius.....	28	5 (17.8 per cent)	7	3 (42.8 per cent)	3
Humerus.....	27	4 (14.8 per cent)	7	4 (57.1 per cent)	5
Ulna.....	17	2 (11.7 per cent)	1	1 (100 per cent)	1
Ununited knees..	9	1 (11.1 per cent)			
Jaw.....	9	1 (11.1 per cent)			
Patella.....	2				
Nose.....	1				
Sacro-iliac.....	1				
Total.....	201	20 (9.9 per cent)	46	19 (41.3 per cent)	15 (6 per cent)

There were thirty-nine (15.7 per cent) infections in the entire 247 cases. In the 201 cases in which there had not been any previous infection there were twenty (9.9 per cent) infections. In the forty-six cases in which there had been previous infection there were nineteen (41.3 per cent) infections.

In the entire group of 247 patients with ununited fractures 223 were traced. Basing end results on these it is found that 177 patients (79.3 per cent) were successfully treated and forty-two (18.8 per cent) were not cured. Eighteen of the patients were operated on twice, making 241 operations on 223 patients with a resulting cure of 177 (73.4 per cent). An attempt to study the failures by percentages is not enlightening, since the causes of failure are many and diversified. Infection is a prominent cause of failure, but does not necessarily mean failure. Faulty technic, poor coaptation of the fragments to each other and to the graft, poor external fixation, and lack of coöperation on the part of the patient may all tend to put undue stress on the graft and cause its fracture. In not a few instances when this has happened in my experience union eventually occurred under proper fixation and control. Osteoporosis of the fragments is an unfavorable condition and should be overcome if possible. More and more I am advising patients with nonunion and osteoporosis to remove all casts or splints and use the part in order to get the bones in better condition to receive the transplant. It is almost a certainty that union will be obtained with the bone graft in a pseudarthrosis of many years' standing when the bone ends are of the eburnated type. This study, therefore, enables me to say that the most favorable bones to deal with in treating ununited fractures are the tibia, ulna, radius, humerus, and femur respectively. The percentage of infections in these cases, contrary to the infections

in the spinal graft cases, is high, and this should be explained. In our 247 cases there were thirty-nine (15.7 per cent) infections following operation. It is only fair, however, to divide these cases into two groups: those in which there had been no infection previously and those in which there had been infection. In 201 cases twenty (9.9 per cent) of clean cases not infected previously, but often having much scar tissue, were infected, whereas in the forty-six cases infected previously nineteen (41.3 per cent) were infected. This rate could be excused possibly in the cases infected previously, but cannot be so readily excused in the clean cases. There are certain extenuating circumstances. Most of the operations were difficult and prolonged, which means that tissues were handled, traumatized, exposed, and often dried more than is proper. The technic is often somewhat difficult of application, particularly when previous operations have produced much scar tissue, and one of the fragments is short and near a joint. These are, I think, the main causes of the high percentage of infection, for the rate of supuration in the easily conducted and short operations on the spine is quite low and will compare with any series of clean cases in the entire field of surgery. In the general surgical cases in the Mayo Clinic Sistrunk has found that the average of infection is about 10 per cent in clean cases, which include all cases clean before operation and retroperitoneal cases not drained. Our technic has not absolutely prevented the introduction of the gloved hand into the wound, but so far as was practical the actual handling of the tissues was done with instruments. I am quite sure that the percentage of infections in the same type of cases would be much higher if the autogenous bone graft were abandoned and beef bone or metal substituted. Metal is irritating to the tissues and beef bone is not as readily tolerated as an autogenous graft. Infection in not a few cases developed because of breaking down of the scar tissue in the deep structures and occasionally because the skin sloughed. The possibility of a hematogenous infection should also be considered. The traumatizing of the tissues incident to the operation causes them to be devitalized and therefore susceptible to infection.

The manner in which the bone graft is used is also of prime importance. In our earlier work the intramedullary plug was used with indifferent success. The inlay graft is as nearly as is possible an anatomic approximation of tissues which appeals to one as being a surgically sound procedure. In a certain percentage of cases, however, in which the operation had been satisfactory in every respect and the post-

operative fixation was as nearly perfect as possible the graft broke, usually about the fifth to the eighth week. I think we are nearly all agreed that the bone transplant at least in great part is absorbed and replaced by new bone. During this period of absorption and replacement there is a period when the graft itself is weakened by the absorption and the new bone deposited is too soft and fresh to be of any real support. At this time a slight stress will cause fracture of the graft. If the massive graft is used the very size of the graft gives a margin of safety not given by either the intramedullary or the inlay graft. Also the cancellous or endosteal tissue is the richest in osteoblasts. By denuding the fragments and exposing the layer of cancellous tissue, and applying the bone graft with its cancellous tissue to that of the fragments, large surfaces rich in osteoblasts are brought together. I believe that with the technic of firmly holding the transplant to the fragments with beef bone screws a large proportion of the transplant functions and lives without being absorbed and replaced by new bone.

I am certain that our results have been improved by using the massive graft and clamping it to the fragments by aid of beef bone screws, and where there is sufficient muscle and soft tissue comfortably to cover it I shall continue to use it. The size of the massive graft in the tibia increases the tension on the skin, and may cause a necrosis of the skin and the death of the graft because of exposure. In the tibia I prefer to use the inlay graft from the opposite leg if the bone is osteoporotic; if not, I use the sliding inlay reversible method.

SUMMARY

The cases studied comprised 413 patients subjected to the operation of transplantation of bone. One hundred sixty-six of the patients were operated on, according to the method of Albee, for tuberculosis of the spine, and 247 were operated on for ununited fractures, bony defects, and so forth. One hundred thirty-two patients with tuberculosis of the spine operated on more than eighteen months before have been definitely followed. Sixty-six (50 per cent) may be regarded as cured or as having the disease arrested; twenty-nine (22 per cent) were improved; twenty-two (16.66 per cent) were unimproved; twelve (9 per cent) died later, probably of disseminated tuberculosis; three (2.26 per cent) died so soon after operation that their deaths must be classified as operative mortalities. The operation is advised only for adults.

Four (2.4 per cent) developed infection in the wound in the spine; there were no infections in wounds of the leg. Two grafts were lost.

Two hundred twenty-three of the 247 patients operated on for ununited fractures and so forth were traced. In 177 (79.3 per cent) the operations were successful, and forty-two (18.8 per cent) were failures. Four (1.7 per cent) died. Two hundred forty-one operations were necessary to obtain these successes; thus the 73.4 per cent successes are based on the number of operations rather than on the number of patients. In contrast to the spinal cases which were better than the average in any group of clean cases the percentage of infections ran high. Thirty-nine (15.7 per cent) of the 247 patients developed infections. Two hundred one had clean wounds at the time of operation. Many of them had been operated on before without suppuration, but often with considerable scarring, twenty (9.9 per cent) of these became infected. Forty-six patients had been infected previously, although apparently the wounds were clean at the time of operation, and in nineteen (41.3 per cent) suppuration followed surgical interference. These infections caused the loss of the graft in fifteen cases (6 per cent) and in almost all a persistence of the nonunion. The technic used in the spinal transplants was used in the fracture transplants. In the first group the percentage of infections is considerably below normal, whereas in the second group the percentage is above normal. I believe, therefore, that the cause of the infections rests on the type of case rather than on the technic. It is possible that a two-stage operation would lower the percentage of infections.

The success in operations on the various long bones was: tibia 89.4 per cent, ulna 81.2 per cent, radius 78.4 per cent, humerus 69.6 per cent, and femur 57.5 per cent. The massive graft with beef bone screws to hold it in place has given better results than either the intra-medullary or the inlay graft.

INGUINAL HERNIOTOMY UNDER REGIONAL ANESTHESIA—A NEW METHOD OF FIELD BLOCK*

GASTON LABAT AND WILLIAM R. MEEKER

It is usually conceded that local anesthesia had its beginning in 1884 when Koller demonstrated the anesthetic action of cocain by instilling a 2 per cent solution into the conjunctival sac. Ophthalmologists were thus the first to make extensive use of cocain anesthesia; but the fact that any mucous membrane was rendered insensitive by cocain soon led to its use by laryngologists and rhinologists. Rapidly following its success in these fields experiments in other lines of surgical work were carried out, and it was soon found that the injection of cocain solutions in the skin as well as subcutaneously was almost immediately followed by a loss of sensibility to pain. The extensive use of the anesthetic drug, in the absence of any serious study of its pharmacologic action, gave rise to dangerous symptoms and many deaths, probably many more than were reported in the literature. Reclus and Schleich did much to overcome these drawbacks by the introduction of weaker solutions; but the type of anesthesia thus produced was inferior to that obtained with the original solutions. Adrenalin solution 1 : 1000 was next added; this prolonged the anesthetic action and decreased the toxicity of the drug, but not to an extent to make even the weaker solutions free from danger.

The possibilities of operating painlessly under local anesthesia were thus demonstrated by the use of cocain and efforts were stimulated to find a substance which on subcutaneous injection would suspend sensation and at the same time be free from toxic effects. As a result a certain number of synthetic products were discovered which possess anesthetic properties and toxicity in greater or less degree. Of these only novocain or procain has proved to be of real practical value. This drug, first produced by Einhorn, in 1905, is readily soluble in water. Its solutions can be sterilized by a limited amount of boiling without

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undergoing any appreciable change. It is not irritating to the tissues and is variously estimated to be seven to ten times less toxic than cocain. Adrenalin added to novocain solutions intensifies the action of the anesthetic drug and lengthens the duration of the anesthesia by contracting the vessels and reducing the rapidity of absorption, so that a much weaker solution is required than when novocain is used alone. The novocain-adrenalin solutions have been proved to be the ideal anesthetic and are employed to cover almost the entire field of operative surgery.

No less striking than the improvement in anesthetic drugs has been the advance in the technic of their administration. The original methods practised by Reclus, Schleich, and Halsted consisted of peripheral intradermal infiltration and massive edematization with a dilute solution. The characteristic feature is that the site of injection lies along the line of incision and in the operative field. This procedure is still employed extensively for minor operations under local anesthesia. Matas and Cushing first reported cases in which operation was performed by a "neuroregional" method, particularly herniotomies, in which there was direct infiltration of the line of incision, and further injection of the parts during operation, in this manner attempting a perineural injection of the nerve trunks encountered at the upper outer extremity of the incision. This method probably remains the most popular among American surgeons who perform herniotomies under local anesthesia. The next important departure came with the circuminjection of the operative field in which a wall of anesthesia is made to encase or isolate the operative area, a procedure known as field block. This principle was probably first practised by Hackenbruch, and later popularized by Braun. True nerve blocking in herniotomy was practiced in 1911 by L  wen, who injected the nerves supplying the inguinal region at their exits from the intervertebral foramina. Thus the trend of progress in technic has been from peripheral infiltration through field block to nerve block, the last being the procedure of choice in all work under injection methods of anesthesia. No matter how large the hernia may be it is sufficient to inject the last three intercostal nerves and the first four lumbar nerves close to their exits from the vertebral column, a procedure known as paravertebral block.⁹ This procedure, however, is technically more difficult than regional block in which the nerves to the operative area are anesthetized farther along their course.

In dealing with major operations, the successful application of regional anesthesia demands patience, time, and skill, skill that can be acquired only through practice on the human skeleton and human cadaver. The operator thus develops a knowledge of anatomy which enables him to visualize the nerve trunks to any region in relation to surrounding structures, especially to the bony prominences of the framework, which are his most reliable landmarks on the living subject. It is for this reason that regional or block anesthesia appeals more forcibly to the well trained surgeon, fresh from the anatomic laboratory, at a time when his volume of operative work is small, and he finds a very practical application for his topographic anatomy, which is a source of no small gratification. It is only through the aid of applied anatomy that regional anesthesia has advanced to its present importance.

It is necessary for the surgeon operating under local methods to use an essentially different technic from that commonly employed under general anesthesia. Speed must often be sacrificed to gentleness. The surgeon should be calm, content, and patient, in spite of occasional short delays. He must be skilled in clean operative dissections and refrain from unnecessarily pulling and handling the tissues. Failure is quite likely to result if the operator is not constantly engaged in this type of work, for he must have learned above all things gentleness, and must have acquainted himself with the sensibilities of the various tissues encountered in various operative fields. The occasional operator who attempts major operations under regional anesthesia often courts failure.

It is important to inform the patient beforehand of the method of anesthesia to be employed, especially of its advantages to himself. He should understand that the operation requires intelligent coöperation for his benefit. It should also be explained that when anesthesia appears he will experience a sensation of weight and numbness in the region blocked and that pull and pressure of the parts may be felt, but that none of these sensations will be painful. The nervous apprehension natural in a patient about to undergo an operation may be allayed by a preliminary hypodermic injection of morphin, one-sixth grain, and scopolamin, one-three-hundredth grain, an hour before the induction of anesthesia. A drowsy, tranquil mental state is thus substituted for one of uneasiness. A patient should, then, not be surprised by being stuck with the needle when he is not expecting it; he should be informed when the needle is to be introduced.

The chief advantage of regional anesthesia over general narcosis is its greater safety.⁶ Inhalation narcosis, especially ether, is ordinarily followed by nausea and vomiting, apart from the possibility of lung complications, thus provoking considerable strain on the abdominal wall with consequent local pain and danger of overstraining the sutures and compromising the result. With regional methods, nausea, if it is present at all, is slight, there is no gaseous distention, and vomiting seldom occurs, thus leaving the sutures undisturbed. The diet of the patient need not be interfered with, as there are no disturbances of the gastro-intestinal tract. A light meal may be taken before operation, if operative conditions permit, and in most instances normal diet may be continued immediately after; in more severe cases it may be restored progressively in from one to three days after operation, according to the general condition of the patient and the type of operation performed. Stimulating drinks, such as coffee, may be administered immediately after operation. Regional anesthesia thus avoids or considerably reduces the postoperative complications often produced by general narcosis, and as a result convalescence is shorter. Even after extensive herniotomy and repair under local anesthesia there is no disturbance of the pulse rate and blood pressure, and since the drugs employed at present do not have any deleterious effects on the kidneys, postoperative renal conditions usually do not occur. It is a great satisfaction for all concerned to have the patients come from the operating room feeling as bright as when they entered it.

The method of regional anesthesia detailed herein has been devised to produce adequate anesthesia for all types of herniotomy and repair, no matter what individual modification in operative technic is adopted. The anesthesia is entirely distinct from the operation proper and is usually induced in a separate room, the patient being entirely anesthetized and ready for operation on entering the operating room. The operation is, therefore, performed without loss of the surgeon's time and there is not the predisposition to infection from prolonged exposure of the wound, as in local infiltration.⁸ Anesthesia remains complete for from one and one-half to two and one-half hours, so that the surgeon is rarely interrupted to make additional injections. The edematization of local infiltration also distorts the operative field,⁵ and the loss of solution considerably reduces the duration of anesthesia, frequently necessitating further injection for the closure. In some instances there is a persisting serous discharge from the wound for two or three days⁷

which prevents healing by first intention and predisposes to infection,⁸ a disadvantage which does not occur with the regional method. Keep-

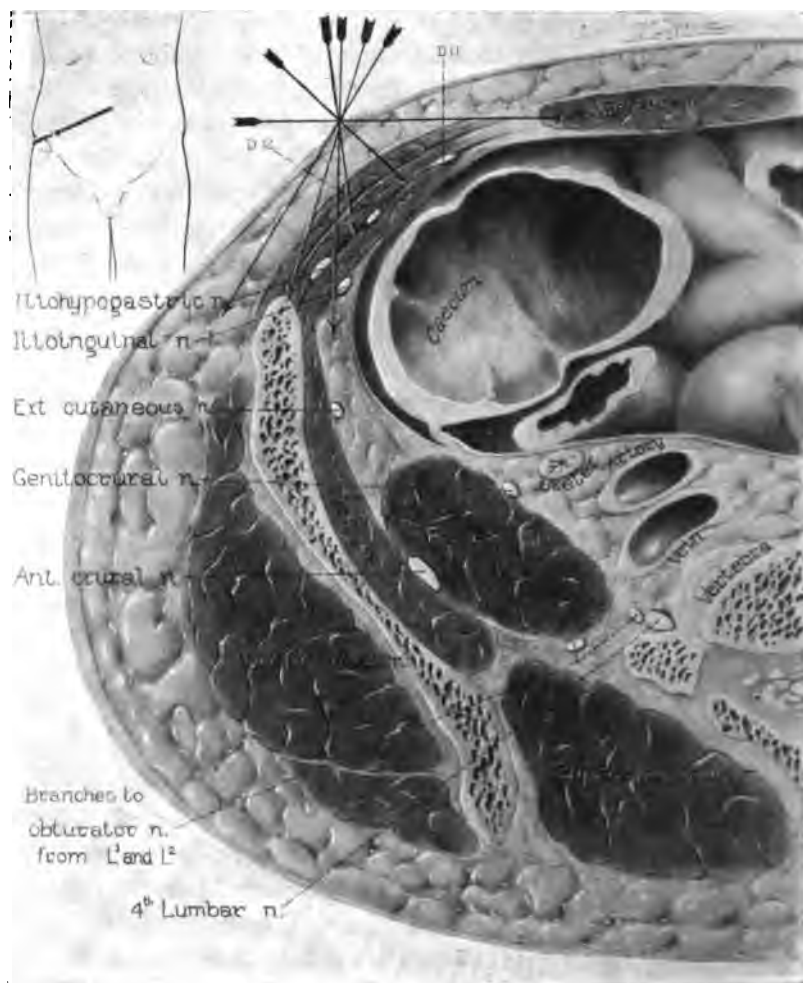


FIG. 332.—Right half of oblique cross-section of the abdomen passing through a point about 2.5 cm. above and medial to the anterior superior spine of the ilium and umbilicus. Note the nerves and the manner of injecting through the para-iliac wheal 1. in Figure 336.

ing the solution away from the operative field also means anesthetization of a larger area which permits greater retraction of tissues because of the greater muscular relaxation.

If a wall of anesthesia is created obliquely across the anterior abdominal wall passing through a point about 2.5 cm. above and medial to the anterior superior spine of the ilium and the umbilicus, the entire nerve supply of the operative area will be cut off, with the exception of the genitofemoral or genitocrural. At that level the eleventh and twelfth thoracic nerves as well as the iliohypogastric nerve lie between the transversus abdominis and the obliquus internus muscles relatively close to the iliac crest. The ilio-inguinal nerve is still in the retroperitoneal tissue beneath the transversus abdominis muscle and at about the same level as the iliohypogastric nerve (Fig. 332). The genitocrural nerve is only accessible at the internal inguinal ring where it emerges with the spermatic cord.

TECHNIC

Unilateral reducible hernia.—Anesthesia is usually induced with 100 c.c. of 0.5 per cent and 50 c.c. of 1 per cent novocain solutions in separate containers. Ten minims of adrenalin solution, 1 : 1,000, are added to each 100 c.c. Less solution is used for a lean patient. If the patient is very obese about 50 c.c. more of the 0.5 per cent solution may be required, but in the average case a total of 150 c.c. is never exceeded. The special regional anesthesia syringe and needles introduced by Labat (Figs. 333, 334, and 335) are employed. The patient is placed in the dorsal decubitus position and the skin prepared as for laparotomy. The operator stands on the side of the region to be anesthetized, and with the smallest needle an intradermal wheal is raised at 1 about 2.5 cm. above and medial to the anterior superior iliac spine; this is called the para-iliac wheal (Fig. 336). A second wheal is raised at 2, which lies just above the pubic spine; this is called the pubic wheal. The subinguinal wheal at 3 lies just below the inguinal (Poupart's) ligament and lateral to the femoral artery. With a needle 8 to 10 cm. long and with an equal mixture of the 0.5 and 1 per cent novocain solutions fanwise injections are made down to the transversalis fascia in a plane perpendicular to the surface of the skin and extending from the crest of the ilium toward the umbilicus, the last injection being made just within the rectus sheath (Fig. 332). A subcutaneous injection then made in this plane creates a wall of anesthesia which blocks the ilio-inguinal, iliohypogastric, and lower two thoracic nerves. Injection should be slow, steady, and continuous as the needle advances and is withdrawn. From 50 to 60 c.c. of solution is used in this injec-

tion in the average case. The needle is next introduced at the pubic wheal 2, and deep injections into the pubic attachment of the rectus muscle on the same side are made, extending a little beyond the middle line, with about 5 c.c. of the solution. Through the same wheal injec-

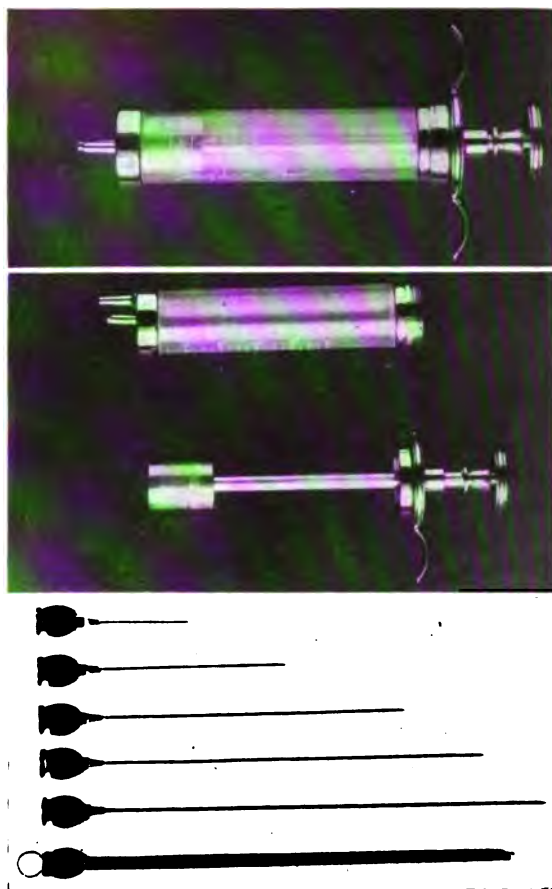


FIG. 333.—Ten cubic centimeter special regional anesthesia syringe.

FIG. 334.—Syringe with two parts disconnected.

FIG. 335.—Special regional anesthesia needles.

tions are made along the horizontal ramus of the pubis to a point 3 to 4 cm. beyond the middle line, about 5 c.c. of solution being employed for this also in the average case. The needle is next introduced at the subinguinal wheal 3, deep injections are made underneath the inguinal ligament, followed by subcutaneous injections parallel with and along

this ligament. The purpose of this injection is to control overlapping branches coming from the anterior crural and external cutaneous nerves and permit greater pull on the inguinal ligament in the approximation of the deep layers. About 10 c.c. of the 0.5 per cent solution is needed for this.

If the hernia reduces spontaneously in the supine position, or if reduction maintains after taxis, the cord structures are next grasped between the thumb and index finger of the left hand at the external ring, or at the point the cord crosses the pubis, and the needle inserted

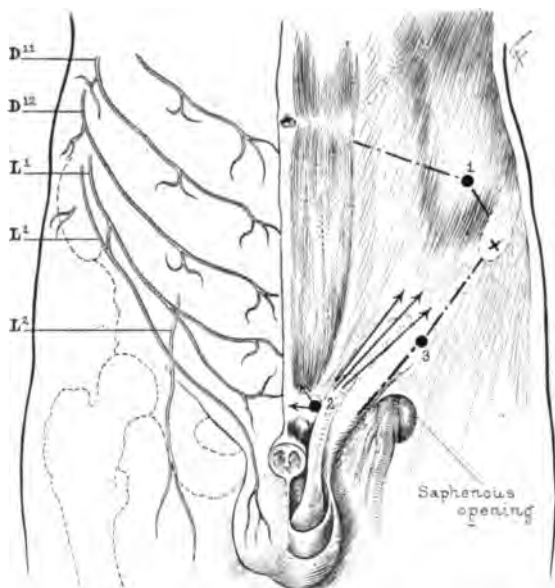


FIG. 336.—Inguinal field block for reducible inguinal hernia: 1, Para-iliac wheal. 2, Pubic wheal. 3, Subinguinal wheal. Note injections of the internal ring from the para-iliac wheal.

through the pubic wheal. The position of the operator for the injection of the cord depends on the side to be injected, the injection being best made from the pubic spine upward. The cord structures are transfixated and injected with about 5 c.c. of the 1 per cent solution, care being exercised not to traumatize the cord structures by multiple punctures, causing hematomas, which, however, are of no clinical importance. The cord is then massaged a little so as to hasten the diffusion of the solution.

The last injections are made at the margins of the internal ring.

If the internal ring is easily found by the palpating finger the needle is advanced from the pubic wheal in the subcutaneous tissue to a point just medial to the margin of the ring. The fascia is then perforated at this point and the injection made. Similar injections are made above and lateral to the margins of the internal ring, 5 to 10 c.c. of the 1 per cent solution being used. If the internal ring cannot be located by palpation, the injections are made midway between the pubic and anterior superior iliac spines about 2.5 cm. above the inguinal ligament. These injections surround the neck of the sac and are meant for blocking the genitofemoral nerve, but failure to anesthetize this nerve oc-



FIG. 337.—Manner of injecting the cord while maintaining reduction with the last three fingers of the left hand.

casionally happens, thus necessitating its injection after exposure of the cord.

Occasionally the reduction of the hernia is not maintained of itself, even with the patient in the supine position, the mass reappearing as soon as the pressure is released. In such cases reduction is maintained with the last three fingers of the left hand while the cord is grasped with the thumb and forefinger and injected as previously described (Fig. 337). The injections around the internal ring are here best made from above through the para-iliac wheal in order to prevent a possible puncture of the sac and its contents.

Bilateral reducible hernia.—Figure 338 illustrates the bilateral block which is based on the principles described for unilateral herniotomy.

The quantity of solution is 200 c.c. of the 0.5 per cent and 50 c.c. of the 1 per cent, with 20 drops of adrenalin in all. If more solution is required for very obese patients, the 0.5 per cent solution is preferable

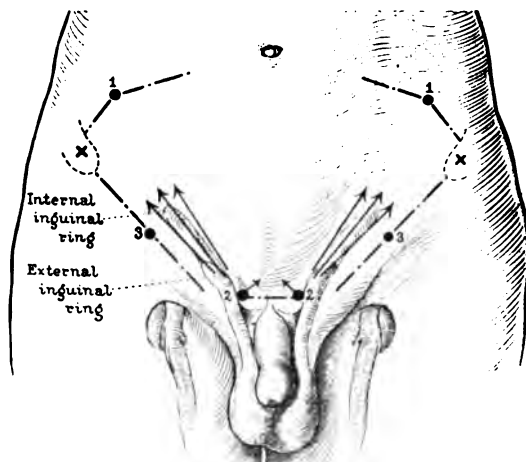


FIG. 338.—Bilateral inguinal field block.

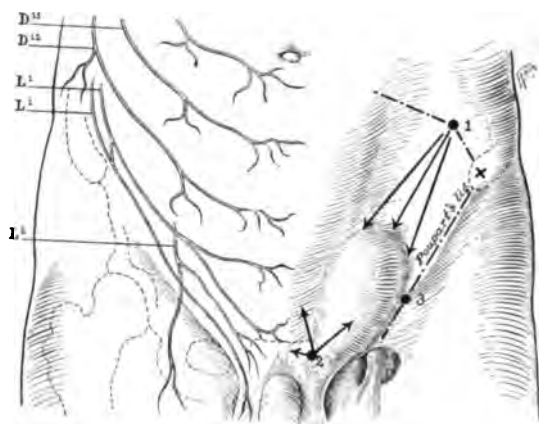


FIG. 339.—Left inguinal field block for irreducible hernia: α , Anterior superior iliac spine. 1, Para-iliac spine. 2, Pubic wheal. 3, Subinguinal wheal. Note nerve distribution on the right side.

to the 1 per cent. The operation should be started on the side first injected. The results are identical with those obtained from unilateral block. Spinal novocainization is much easier and quicker, but the duration of the anesthesia is only from one to one and one-half hours.

Irreducible hernia.—In irreducible hernia a different technic is employed to meet the resulting distortion of the region. Wheals 1, 2, and 3 are raised at exactly the same points as in cases of reducible hernia, unless the deformity of the region renders palpation of the pubic spine impossible, in which case the pubic wheal 2 is raised on either side of the hernial mass, but always level with the pubic bone. Wheal 3 (Fig. 339) is at the lateral margin of the hernial mass just below the inguinal ligament and lateral to the femoral artery.

Injections through the para-iliac wheal 1, located about 2.5 cm. above and medial to the anterior superior iliac spine, are made essentially as already described. Injections through wheal 2 are made along the horizontal ramus of the pubis and in the pubic attachment of the rectus muscle on the same side, but great care should be exercised not to transfix the hernial mass. Injection of the cord through the pubic wheal is not safe unless the parts held between the thumb and index finger at 2 are composed essentially of the structures of the cord. If there is any doubt of the presence of the sac among the structures grasped, deep injections, as well as subcutaneous injections, are made in the direction of the arrows from 2, on both sides of the hernial mass, retracting the mass with the left hand to avoid its puncture. The cord is injected after exposure. Usually the genitocrural nerve cannot be injected from the pubic spine 2, but the neck of the sac is infiltrated from 1, as shown by the arrows; other injections are seldom necessary after exposure of the sac.

Strangulated hernia.—A diminution in sensibility to pain accompanies strangulations, this is probably due to compression of the nerves and alteration in the blood supply of the strangulated area. Simple infiltration along the line of incision is all that is necessary; deeper injections depend on the pathologic changes of the hernia and of the surrounding structures.

Inguinoscrotal and recurrent hernia.—The same procedure is used as for unilateral inguinal herniotomy, but in old inguinoscrotal or sliding and recurrent hernia the cord structures are particularly difficult to block. It is, therefore, best to inject them after exposure, unless the injections at the internal inguinal ring from the para-iliac wheal have been successful. With the inguinal incision it is not necessary to circuminject the base of the genitalia, as proposed by Braun, Pauchet, and others. Spinal novocainization is preferred in these cases, and when properly administered is quite as safe as the regional field block.

A little more time is required for regional anesthesia than for the induction of general narcosis, but the advantages of the method greatly compensate for this insignificant loss of time. Usually no further injections are required, and no pain is experienced by the patient, provided the proper surgical technic is employed. A gentle, unhurried and quiet technic is imperative, especially in dealing with the hernial sac. If the hernia is long standing, and especially if the patient has worn a truss, the adhesions are apt to be more extensive. The scalpel instead of the scissors is used for all necessary separation of such parts. Pulling and tearing are detrimental both to the patient and the method. After the sac has been opened the contents may be pushed through the internal ring without causing pain if it is done gently. If no pull or tension is exerted adherent omentum and intestines may be separated painlessly on the accompanying mesentery. Pain in inducing the anesthesia is so slight that it need not be considered; it is caused principally by the initial entrance of the needle into the skin to raise the intradermal wheals. The complaint during operation, if any, is often from the cramped position and the tired feeling from lying on a hard table. The table should be well padded and there should be a comfortable pillow for the patient's head. His position should be easy and comfortable so that he will not wish to move for an hour. A tactful assistant should sit by the patient's head and engage him in conversation, sponge his face, administer small sips of water, and in other ways contribute to his mental ease. Nervous apprehension may also be quieted by a calm demeanor on the part of the surgeon and his assistants.

Indications.—There are no contra-indications to the use of regional anesthesia except possibly in the very young patient. The regional method is particularly indicated in patients who have cardiac trouble, nephritis, pulmonary disease, or any other condition that is not favorable to general narcosis, such as high blood pressure and diabetes. In the excessively obese patient spinal novocainization is preferable, because of the difficulty in injecting the deeper structures through the fatty layers. For strangulated hernia regional or local anesthesia is imperative, since the patient is in a very bad condition generally, and the added load of one-half hour to an hour under ether certainly should be avoided.

CONCLUSIONS

1. Regional anesthesia with novocain adrenalin solution is the method of choice in inguinal herniotomy and should be used generally instead of only for patients who are unsafe subjects for general anesthesia.

2. For inguinoscrotal or for bilateral herniotomy in very obese patients spinal novocainization is easier and quicker and as safe as regional field block.

3. A hypodermic of morphin and scopolamin one hour before anesthesia is induced is of aid in calming nervous apprehension.

4. The patient should be informed beforehand of the method and its advantages.

5. It is necessary that the surgeon's technic be gentle and unhurried.

6. Every possible detail contributing to the comfort of the patient should be utilized.

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GENERAL

STUDIES OF THE METABOLISM OF DIABETES*

RUSSELL M. WILDER, WALTER M. BOOTHBY, AND CAROL BEELER

The chart (Fig. 340) and table presented give the more important data of metabolism experiments in a case of diabetes of great severity. The patient, Bessie B., was an unmarried woman, twenty-eight years of age. Her diabetes, the severe acute type, was of two and one-half years' duration. She was a good subject for metabolic study. Her patience was exemplary and the nervous irritability and restlessness which often vitiate investigations on patients with severe diabetes were therefore avoided. The diabetes was not complicated by any other disease or by any demonstrable infection either acute or chronic.

The present study was stimulated by observations of Lusk and Allen and DuBois, which emphasized the deleterious effect of high protein dietaries in diabetes, as well as by the studies of Newburgh and Marsh which seem to demonstrate the therapeutic value of diets low in protein and relatively high in fat. The experiments were planned to throw light on questions of therapeutic and theoretic interest as follows:

1. Has the feeding of protein any specifically deleterious action on the mechanism of sugar utilization other than that which can be explained by its calorific value or by the sugar or acetone bodies theoretically derivable from it and thrown upon the metabolism by its ingestion?

2. Is the *basal* metabolic level of a *diabetic* individual affected by food, and if so, how much of this effect is attributable to the calorific value and how much to the protein of the food?

The foods used were as simple as the length of the periods of observation permitted, consisting of green beans, asparagus, tomatoes, eggs, cream, butter, beefsteak, and soy bean bread. Metabolic rate examinations were made by the gasometer method as described by Boothby

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and Sandiford. The daily rate of sugar utilization was calculated from the urinary excretion of nitrogen and dextrose and the carbohydrate

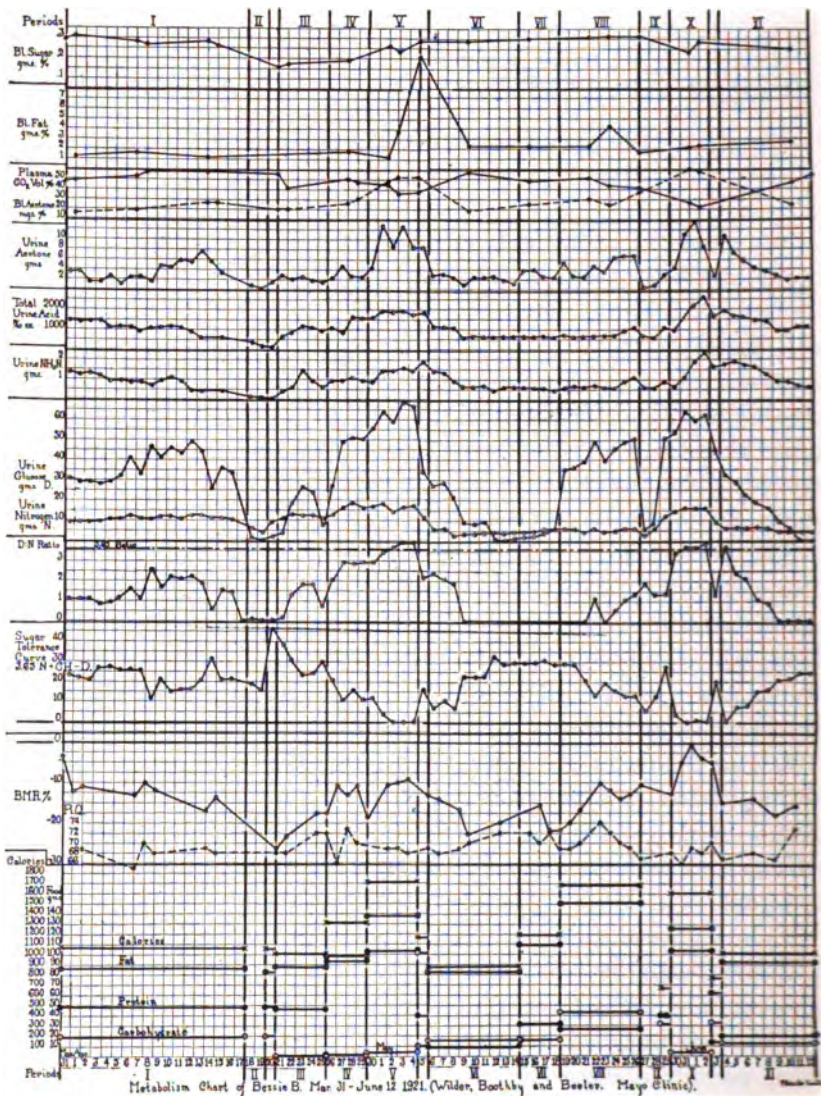


FIG. 340.

value of the food as follows: the number of grams of nitrogen in the urine was multiplied by 3.65 to give the number of grams of sugar derived from katabolized protein, to the product was added the num-

ber of grams of carbohydrate in the diet and from this sum the number of grams of dextrose in the urine was subtracted. The dextrose-nitrogen ratios of the urine were calculated by subtracting the carbohydrate of the food from the glucose value of the urine in grams, and dividing the remainder by the number of grams of nitrogen in the urine. We are aware that many persons will not accept the validity of D/N ratios obtained with diets containing carbohydrates. The objection does not seem valid under such circumstances as existed in these experiments in which daily observations were conducted for a long period. However, in order to eliminate objections on this score as much as possible, the diets of Periods III, IV, V, and X were constructed with insignificant amounts of carbohydrate.

In Period I of eighteen days the diet contained 19.9 gm. of carbohydrate, 48.8 gm. of protein, and 85.5 gm. of fat; 1,077 calories. The patient had been living at home on this diet for four months. The glucose excretion for the period of observation averaged 37 gm. and nitrogen excretion about 11 gm. The D/N ratios averaged 1.52, and the utilization of glucose from all sources did not exceed 30 gm., and much of this time was as low as 22 gm. a day. A slight acidosis existed as is shown by ammonia nitrogen excretions of over 1 gm. and by total acetone bodies of over 3 gm. daily. The blood sugar remained above 0.266 per cent. The basal metabolic rates for eight determinations averaged -12 per cent. These preliminary observations were followed by two days of starvation, April 17 and 18. April 19, the patient was placed on her previous diet. The beneficial effect of this fast was striking, confirming the general belief in the therapeutic value of an occasional fast day in the management of diabetes.

In Periods III, IV, and V no carbohydrate was allowed except the gram or two derived from the soy bean bread. In Period III the amount of protein and fat consumed was practically the same as in Period I. In Periods IV and V the allowance of protein was increased to 94.2 and 103.6 gm. and the fat raised to 99.1 and 137.9 gm. respectively. The effect of such increase was apparent at once. The basal metabolic rate rose from an average of -20 per cent for three determinations between April 22 and 26 to an average of -14 per cent between April 27 and 30, and finally to an average of -10 per cent between May 1 and 4. In a parallel manner the D/N ratio increased rapidly to 3.65, which Lusk has considered to indicate the state of complete diabetes.

Accompanying these changes, but definitely lagging behind them, were increasing acetone formation and evidence of acidosis in the declining carbon dioxid combining power of the plasma and the rising total acidities of the urine. May 4, clinical symptoms of threatening coma forbade prolongation of the period.

Beginning with the noon meal of May 5 and during Period VI, the diet contained 15.6 gm. of carbohydrate, 9.9 gm. of protein, and 83.4 gm. of fat. This diet is similar to those employed by Newburgh and Marsh. Its therapeutic result on this completely diabetic patient with increasing acidosis and impending coma was very satisfactory. Within seven days the urine became sugar free and ketogenesis was controlled. Simultaneously, the basal metabolic rate fell rapidly to an average of -20 per cent for the last two days of the period. In Period VII the protein allowance was increased to 30.7 gm. and the fat to 109.1 gm. Traces of sugar reappeared in the urine, but otherwise the favorable clinical condition of the patient remained unchanged. The sugar utilization for these four days averaged 29.7 gm.

If we attempt to analyze the effect of the protein in the high protein diet of Period V on the basal metabolic level and the sugar utilization, it is obvious that four factors must receive consideration: (1) the high calorific value of this diet; (2) its high glucose value (glucose derivable from protein); (3) its high ketogenic value (aceto-acetic acid derivable from protein and fat), and (4) a possible specific effect of the protein per se.

In order to throw light on the relative significance of the protein factor, the diet of Period VIII was constructed so as to be comparable to that of Period V in calories, in glucose value, and in ketogenic value. The only significant difference between the two diets was in the amount of protein. Whereas 103.6 gm. of protein were included in the diet of Period V, there were only 26.5 gm. in the diet of Period VIII. Inasmuch as this smaller amount of protein would yield a smaller amount of glucose, an additional 42.6 gm. of carbohydrate was included in the diet of Period VIII. In Period X, a diet was given which was practically the same as that of Period V, but agreed a little more closely in ketogenic value to the diet of Period VIII.

If, now, the data of these three periods are compared, it will be seen that the low protein diet of Period VIII was tolerated much more satisfactorily than the high protein diets of Periods V and X. Sugar reappeared in the urine in large amounts, nevertheless, appreciable

sugar utilization continued, and even after eight days the D/N ratio did not exceed 1.35. In Periods V and X complete intolerance for sugar resulted almost immediately after the ingestion of the high protein meals, indicated by the D/N ratios. The average basal metabolic rate in Period VIII was -14 per cent. This is 4 points lower than that of Period V and 10 points lower than the level of Period X.

In Period XI the diet was designed to provide not more than 0.66 gm. of protein for each kilogram of body weight, fat in sufficient amount for adequate calories to maintain the patient at rest, and carbohydrate equal to, but not exceeding, the patient's tolerance for glucose as previously determined. The calorific value of this food was somewhat higher than that of the food in Period VI. In other respects the two diets are very similar. As before, glycosuria and ketosis were controlled without difficulty. Sugar disappeared from the urine within eight days and the ferric chlorid reaction of the urine was negative on the sixth day.

CONCLUSIONS

1. The postabsorptive or basal metabolic level of the diabetic patient is materially affected by the previous diet. In the undernourished patient it may be found as low as 32 per cent below the DuBois normal standard. The ingestion of 3 gm. of protein for each kilogram of body weight each day caused a greater rise in the basal metabolic rate than occurred with isocaloric amounts of other foods. Accumulation of the specific dynamic action of protein seemed to account in the main for the elevation of the basal metabolic level which occurred.

2. The rate of sugar utilization of this diabetic patient was depressed by high calorie diets, being much more markedly depressed by protein than by isocaloric amounts of fat. This protein effect was not primarily due to the sugar and ketogenic substances, which the ingestion of protein throws on the metabolism, but to some other more specific action of protein.

3. Throughout this series of experiments the rate of sugar utilization varied inversely with the basal metabolic level of the patient, rising as the basal metabolic rate fell, and vice versa. This behavior suggests a definite interrelationship of the two, and the fact that ingested protein elevates the basal metabolic rate makes it seem possible that the specific depressing action of protein on the mechanism of sugar utilization may be by means of its elevation of the metabolic level.

TABLE 1
METABOLISM DATA IN A CASE OF DIABETES

Date, 1921.	Food intake.				Twenty-four-hour specimen of urine.										Blood.					Respiratory metabolism.					Period.
	Carbohydrate, gm.	Protein, gm.	Fat, gm.	Total calories.	Nitrogen, gm.	Glucose, gm.	D/N ratio.	Acetone bodies as acetone, gm.	Ammonia nitrogen, gm.	Phosphates as phosphorus, gm.	Nitrogen balance, gm.	Sugar, gm., 100 c.c.	Acetone bodies as acetone, mg., 100 c.c.	Fat, gm., 100 c.c.	Carbon dioxide volumes, per cent.	Total calories for each hour.	Basal metabolic rate per cent. DuBois standards.	Respiratory quotient.	Nonprotein respiratory quotient.						
4/15	19.9	48.8	85.5	1077	9.29	20.55	1.15	5.56	1.32	0.905	-1.48	394	..	1.35	47.0	39.2	43.2	0.68	0.63	31.5					
4/16	19.9	48.8	85.5	1077	8.76	20.45	1.10	5.56	1.26	0.841	-0.53	303	.15	..	49.4	39.8	44.1	0.68	0.63	31.5					
4/17	19.9	48.8	85.5	1077	8.71	20.45	1.10	5.56	1.26	0.899	0.90	..	..	..	49.4	40.1	44.1	0.69	0.68	31.7					
4/18	19.9	48.8	85.5	1077	9.92	28.40	0.87	1.56	1.18	0.911	2.01	..	..	..	..	..	..	..	..	..					
4/19	19.9	48.8	85.5	1077	10.05	29.05	0.91	2.45	0.95	0.927	2.94	..	..	..	..	..	..	..	..	..					
4/20	19.9	48.8	85.5	1077	10.96	32.40	0.91	2.45	0.95	0.95	2.95	..	..	..	..	..	..	..	..	..					
4/21	19.9	48.8	85.5	1077	13.92	41.55	1.64	1.20	0.89	1.17	5.41	..	..	..	..	..	..	..	..	..					
4/22	19.9	48.8	85.5	1077	10.65	33.10	1.24	2.05	0.82	0.92	2.64	..	..	..	..	..	..	..	..	..					
4/23	19.9	48.8	85.5	1077	10.77	47.30	0.94	1.84	0.74	1.05	2.96	..	..	..	..	..	..	..	..	..					
4/24	19.9	48.8	85.5	1077	11.65	40.48	1.77	4.48	0.94	1.01	3.84	..	..	..	..	..	..	..	..	..					
4/25	19.9	48.8	85.5	1077	11.35	46.25	2.35	4.11	1.04	1.09	..	..	..	..	..	..	..	..	..	..					
4/26	19.9	48.8	85.5	1077	10.95	43.60	2.15	5.87	0.95	1.04	3.14	..	..	..	..	..	..	..	..	..					
4/27	19.9	48.8	85.5	1077	12.74	49.45	2.92	6.72	0.40	0.83	4.93	..	..	..	..	..	..	..	..	..					
4/28	19.9	48.8	85.5	1077	12.90	44.74	1.94	7.73	0.38	1.15	4.99	..	..	..	..	..	..	..	..	..					
4/29	19.9	48.8	85.5	1077	11.04	36.60	0.61	5.77	0.45	1.03	3.93	..	..	..	..	..	..	..	..	..					
4/30	19.9	48.8	85.5	1077	10.92	36.90	1.55	5.38	0.45	0.99	2.71	..	..	..	..	..	..	..	..	..					
4/10	19.9	48.8	85.5	1077	10.76	33.90	1.40	..	..	..	2.10	..	..	..	..	..	..	..	..	..					
4/11	19.9	48.8	85.5	1077	10.74	37.00	1.59	..	..	..	2.95	..	..	..	..	..	..	..	..	..					
4/12	0	0	0	0	5.68	1.25	0.92	0.95	0.17	..	..	..	..	..	..	..	..	..	..	..					
4/13	0	0	0	0	4.43	..	..	0.99	0.13	0.43	..	..	..	..	..	..	..	..	..	..					
4/14	19.9	48.8	84.6	1069	8.08	2.56	..	1.58	0.80	0.80	-0.57	..	..	..	..	..	..	..	..	..					
4/21	0.7	46.9	88.3	1016	11.54	4.00	0.29	2.85	0.27	1.03	4.04	168	20	..	56.6	34.1	37.0	0.68	0.64	34.1					
4/22	0.7	46.9	88.3	1016	13.45	18.90	1.36	2.80	0.28	0.86	5.83	178	20	..	40.9	34.7	34.7	0.68	0.68	33.3					
4/23	0.7	46.9	88.3	1016	13.47	25.50	1.85	2.83	1.43	1.03	5.77	..	..	..	..	..	..	..	..	..					
4/24	0.7	46.9	88.3	1016	13.25	24.68	1.81	1.80	0.26	1.12	5.73	..	..	..	..	..	..	..	..	..					
4/25	0.7	46.9	88.3	1016	10.43	8.77	0.77	1.89	0.65	1.01	2.93	..	..	..	..	..	..	..	..	..					
4/26	1.8	94.2	99.1	1315	13.00	27.88	2.01	2.83	0.82	1.80	+2.07	..	..	..	..	..	..	..	..	..					
4/27	1.8	94.2	99.1	1315	16.00	49.40	2.98	4.82	0.90	1.93	0.85	..	..	..	..	..	..	..	..	..					
4/28	1.8	94.2	99.1	1315	18.06	51.44	2.75	2.89	1.14	1.97	-2.99	197	86	1.71	50.4	39.5	39.5	0.73	0.63	31.6					
4/29	1.8	94.2	99.1	1315	16.56	50.30	2.96	3.59	0.99	1.40	-1.99	..	..	..	47.0	40.5	40.5	0.70	0.70	32.1					
4/30	3.3	108.6	137.9	1741	17.25	55.30	2.96	4.15	0.88	1.50	-0.97	..	..	..	..	..	..	..	..	..					
5/1	8.8	105.6	137.9	1741	17.98	64.80	3.41	12.85	1.40	1.09	-1.78	266	49	1.81	45.8	39.8	39.8	0.69	0.70	31.7					
5/2	9.3	108.6	137.9	1741	16.85	59.04	3.76	6.62	1.44	1.40	+1.75	..	..	..	..	..	..	..	..	..					
5/3	9.3	108.6	137.9	1741	16.85	64.80	3.76	12.85	1.40	1.09	+0.05	255	28	8.90	36.9	41.4	41.4	0.69	0.71	31.7					
5/4	9.3	108.6	137.9	1741	17.90	67.88	3.98	12.85	1.44	1.04	-0.48	..	..	..	..	..	..	..	..	..					

4. Diets relatively high in fat, but low in protein, and planned to contain nearly two gram-molecules of ketogenic fatty acids to one of antiketogenic glucose on two occasions checked and controlled a dangerous and rising acidosis. The data of the metabolism of two days when acidosis was minimal indicates that on these days the actual ketogenic-antiketogenic ratio in the metabolizing mixture was 1.53 and 1.78 respectively. It is suggested that the proportion of fatty acid which will completely burn with a limited amount of metabolizing glucose is not the same at all basal metabolic levels, but may be increased by measures designed to depress the metabolic level.

THE ETIOLOGY AND LABORATORY DIAGNOSIS OF ACTINOMYCOSIS*

ARTHUR H. SANFORD AND THOMAS B. MAGATH

Actinomycosis is classified among the rarer of the infectious diseases. When a review of the mass of literature on the subject is attempted, however, it appears that the disease is either gradually increasing, or, as is true in other conditions, keener observation has brought about keener diagnoses, so that actinomycetes in man is not an uncommon finding.

The most notable collection of cases that has been reported in this country is that of Ruhrah, who collected sixty-nine cases up to 1900. One of the early important studies of the bacteriology of *Actinomyces bovis* is that by Wright.

The classification of actinomycetes bacteriologically has been the subject of considerable controversy. This is due to the fact that much confusion has arisen in this disease, as in other mycoses, from the inaccuracy of synonyms and the meager description of organisms reported by individual workers. A few attempts have been made to clear up this confusion by careful studies of the group, and of the biologic characteristics of various species. Breed and Conn, in a study of the nomenclature of Actinomycetaceæ, have recommended to the Committee on Characterization and Classification appointed by the Society of American Bacteriologists that two genera be recognized in the family, Actinomyces, with *Actinomyces bovis* Harz as the type species, and Nocardia with no type species named. The first genus is intended to include the anaërobic pathogenic types, and the second to include aërobic species, primarily saprophytic in nature. Breed and Conn have in addenda to this report taken exception to a report by Merrill and Wade, that appeared simultaneously with their first paper, contending that *Discomyces* Rivolta is the correct term to use. Although *Discomyces* Rivolta has priority, *Actinomyces* Harz is given the place of preference through usage. This has been accepted by the Society

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of American Bacteriologists and the term *Actinomyces* has been added to their list of approved genera.

In our selection of cases in the American literature and in the Mayo Clinic series we have discarded cases of infection with acid-fast aerobic organisms, as we believed that these should properly belong to the genus *Nocardia*, and have restricted ourselves to those cases which have been infected with the "ray fungus" or the actinomycetes of the *bovis* type. As a criterion for this standpoint we have the work of Wright and of several others, who have made more recent studies of the bacteriologic characteristics of the disease.

Colebrook, in England, has recently reported a very careful study of actinomycosis in man. He isolated twenty-one strains of actinomycetes of undoubtedly the same group. Two strains were evidently of a different group, and one strain was frankly different from the common type. In all twenty-seven strains of actinomycetes were isolated in twenty-eight cases. This is a remarkable result inasmuch as the cultivation of *Actinomyces bovis* is by no means a simple bacteriologic procedure. The chief point in the cultural characteristics of all strains that are true to type is the strong preference for anaerobic growth, although some strains become capable of aerobic growth if subcultured in broth under a column of liquid paraffin. Glucose is usually necessary for a luxuriant growth of the primary culture. The optimum hydrogen ion concentration is from 7.3 to 7.6. The viability of actinomycetes is slight. They are killed by exposure to 60 C. for one hour, and surface cultures are reported by Colebrook as being sensitive to desiccation. Frequent subcultures tend to kill the strain. They are best kept alive in the ice box when cultivated on egg mediums and when kept moist.

Many divergent views are reported in the literature with regard to the source of infection. We shall not attempt to enter into this controversy. There are a few points of interest, however, in the various theories that have been presented. One of the most common ideas is that the ray fungus is conveyed to man from vegetable sources. Injuries with barley beards or the hard portion of grains or grasses, especially around the mouth, are commonly considered the sources of infection. The instances in which such injuries are reported in the literature are too numerous to mention short of a complete review of the history of actinomycosis. Colebrook, however, has called attention to the fact that there may be some skepticism regarding this view,

as the common organism which is found on vegetable sources is an aërobic fungus which does not usually conform bacteriologically to the type species which is used to describe the group. The anaërobic organism of the type *Actinomyces bovis* has not been demonstrated unquestionably in natural sources outside the animal body.

Another view that is gaining ground is that the organism is a natural inhabitant of the alimentary tract, and that on certain occasions it is carried into the tissues and appears to establish itself there. There are two cases in the literature, one in England (Cope) and one in America (McWilliams) of actinomycosis of the finger resulting from injury inflicted by an opponent's tooth in a fist fight. In both of these cases the inference is that actinomyces was present in the oral cavity of a person who was not suffering from the clinical manifestations of actinomycosis, and that the spores were carried into the tissues through the injury to the finger. Lord, several years ago, demonstrated in carious teeth and tonsillar crypts of normal persons organisms morphologically and tinctorially identical with *Actinomyces bovis*. He was able to produce lesions in small animals by inoculation with the organisms which contained typical clumps of ray fungi. The question of the transference of actinomycetes from animal to man or from man to man has been raised by many writers, but direct proof of this form of transference has not been demonstrated satisfactorily. Indeed, when all the evidence is weighed the true method of infection has not as yet been clearly proved.

LABORATORY METHODS OF DIAGNOSIS

The chief diagnostic finding in actinomycosis is the presence of so-called sulphur bodies in the pus. These are macroscopic and characteristic. While organized bodies in various pathologic conditions may, to a certain extent, simulate the actinomyces granule, the alert observer will be almost sure of his diagnosis when he spies one of the light yellow bodies being carried out in the pus of a discharging sinus (Fig. 341). In the preparation of slides for demonstrating the ray fungus we have found it convenient to use some fluid, either ordinary distilled water, or 20 per cent potassium hydroxid solution, to wash the pus cells away from the granules. This procedure is carried out on the microscope slide. The granule is then crushed with a cover slip and examined at once with the low power of the microscope where the characteristic daisy formation is easily recognized (Fig. 342).

Clumps of inspissated pus have been mistaken grossly for sulphur bodies. However, such material is easily teased out in the distilled water on the microscope slide and disintegrated when a cover slip is placed over it, while the actinomyces granule is so well organized and matted together that sometimes considerable pressure is necessary in order to press it out for examination. The difference in refractivity between the colony and the surrounding material on the slide is very characteristic. When stained preparations are desired the pus is fixed on the microscope slide in the usual manner and stained with Gram's



FIG. 341 (Case A346271).—Sulphur bodies.

stain. The mycelia are gram-positive, while the clumps are more apt to be stained with the counter stain. The filaments on an average are from 10 to 12 microns long, the clumps from 20 to 30 microns long and 8 to 10 microns broad.

The diagnosis of actinomycosis by culture is attended with some difficulty since *Actinomyces bovis* does not grow readily, even under anaërobic conditions. If many cultures are made it is possible to obtain growth from a small percentage of the sulphur bodies that are inoculated deep in the melted agar tubes (Fig. 343). Glucose is usually

necessary for growth. We have had little success in subculturing primary cultures.

Colebrook, who has met with so much success in England in isolating *Actinomyces bovis*, also reported the presence of peculiar accompanying bacilli in all of his cultures that he has called *Bacillus actinomycetum comitans*. It will be interesting in the future to note whether this organism is reported as a common symbiotic organism with *Actinomyces bovis*.

The pathologic examination of the tissue in a carefully prepared specimen will reveal the characteristic ray fungus (Fig. 344). These are best demonstrated with the Gram-Weigert stain.

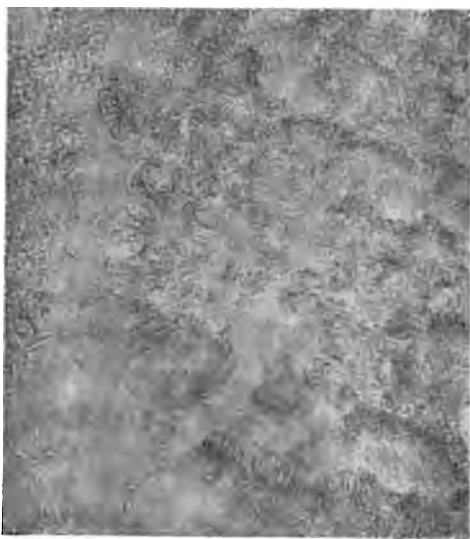


FIG. 342.—Crushed actinomyces granule.



FIG. 343.—Colony of actinomyces in glucose agar.

In discussing the laboratory diagnosis of actinomycosis, mention might be made of the value of roentgenography. There is practically no positive value in this form of examination in the ordinary case of actinomycosis since actinomyces does not involve bony structures. However, in actinomycosis of the lung the shadow might reveal the location of a collection of pus. If ray fungi have been demonstrated in

the sputum this will be of assistance to the surgeon in his operative procedures.

As a further study of *Actinomyces bovis*, serologic tests might be mentioned. Colebrook has reported his observations on agglutinability and agglutinogenic properties of *Actinomyces bovis*, and calls attention to the fact that little is known on the subject. He states that patients heavily infected usually give coarse agglutination with his suspension of *Actinomyces bovis* dilutions of 1 : 500 to 1 : 4,000, a slight infection of the cervicofacial type failing to show agglutination. Similar coarse agglutination was obtained with serums from rabbits inoculated with a vaccine of *Actinomyces bovis*. It has not been demonstrated whether

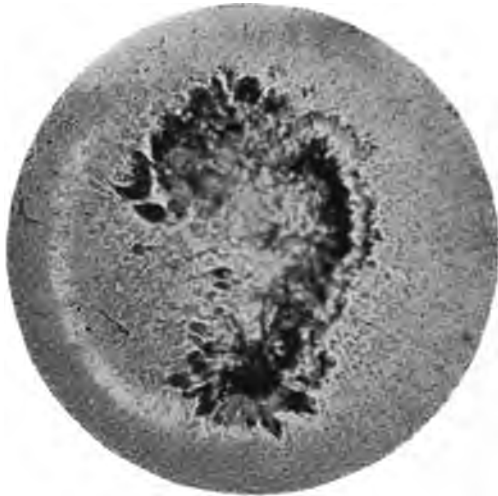


FIG. 344 (Case A210659).—*Actinomyces* in tissue, showing mycelia and clubs.

there are several serologic types of *Actinomyces bovis*. We are also interested in whether pure cultures of this organism may be used as antigens to demonstrate complement fixing bodies in infected individuals, and have planned some investigations of this nature. The possibilities of serology as a means of confirming diagnosis are suggested, although our interest in this subject is chiefly from the experimental standpoint.

We are attempting to review the voluminous literature on actinomycosis, but we believe that it is not feasible to discuss, in this paper, reported cases in detail. We do believe, however, that for the convenience of future workers all the cases reported in the United States

should be collected. We shall report these in another paper, and shall refer here to 119 cases only that are reported to have occurred in the United States. The etiologic factors of these will be compared with the etiologic factors seen in the cases in the Mayo Clinic. Cases of Actinomycosis of the head and neck that have been observed in the Clinic are being studied by New. New and Figi have reported three cases of actinomycosis of the tongue. Brogden has collected fourteen cases of intestinal actinomycosis diagnosed at the Clinic, and his report is ready for publication. Moersch is interested in infection of the nervous system with *Actinomyces bovis* and is about to report three cases that have been seen at the Clinic. Consequently the disease will not be considered from a clinical standpoint in this paper nor do we attempt to discuss methods of treatment.

The first diagnosis of actinomycosis in the Clinic was made in 1909. Since then ninety-six cases have been diagnosed. The basis for the diagnosis in each case has been either demonstration of typical sulphur bodies in the pus coming from the lesion or the demonstration of actinomyces in the tissue by the pathologist. In many instances both criteria have been used for the diagnosis. On the whole, each year shows more cases of actinomycosis than the preceding year, although this should not be construed to be an intimation that actinomycosis is increasing.

Actinomycosis is primarily a disease of the male. Eighty-four of our ninety-six cases were in males. Of the 119 cases collected in which the sex is stated, seventy-nine were in males. Thus it may be concluded that about 80 per cent of the cases occur in males. The reason for this is perhaps evident when suggested modes of infection are taken into account. If it is granted that the common mode of infection is from chewing or ingesting contaminated grass or straw, which is in reality a habit of outdoor life, it is obvious that the male is more often exposed than the female. Likewise if infection occurs through contact with infected cattle, the male is more often exposed than the female. Quite often the females infected are wives of farmers, who possibly share with their husbands the outdoor life of the farm. It is also true that men are more prone than women to neglect the care of the mouth.

The distribution by age is striking. In our series of cases the large majority have occurred between the ages of twenty-five and forty-five years. The age incidence was practically the same in the 119 cases collected, so that it may be stated that actinomycosis is primarily a

disease of middle life. This may be discounted, however, by the fact that persons are most active in outdoor life at this age and may come in contact more often with the source of infection. No age seems to be exempt; in our series were patients of nine and of seventy-one years (Table 1).

That occupation is a factor in the etiology of actinomycosis is quite evident, and has been noted by previous writers. In our series of ninety-six cases fifty-seven were in farmers (Table 2). In the 119 cases collected from the literature sixteen were in farmers (Table 3), but it should be stated that the occupation was not noted in one-fourth of the cases reported. It is likely that in this series, as in ours, infection among farmers predominates. The disease is noted also in stock buyers, ranchmen, stock raisers, leather cutters, and various men who

TABLE 1
NINETY-SIX CASES OF ACTINOMYCOSIS IN THE MAYO CLINIC
Distribution by ages.

Years.	Cases.
1 to 10.....	2
11 to 20.....	10
21 to 30.....	25
31 to 40.....	20
41 to 50.....	22
51 to 60.....	12
61 to 70.....	4
71 to 80.....	1

TABLE 2
NINETY-SIX CASES OF ACTINOMYCOSIS IN THE MAYO CLINIC
Distribution by occupations

Barber.....	1	Meat cutter.....	1
Bookkeeper.....	1	Merchant.....	1
Carpenter.....	2	Minister.....	1
Druggist.....	1	Not known.....	1
Engineer.....	1	Plumber.....	1
Farmer.....	57	Rancher.....	1
Farm implement dealer.....	1	Stock buyer.....	1
Housewife.....	12	Stock raiser.....	1
Justice (Court of Appeals).....	1	Stone cutter.....	1
Laborer.....	5	Telegraph operator.....	1
Leather cutter.....	1	Tile mill worker.....	1
Machinist.....	1		

TABLE 3

ONE HUNDRED NINETEEN CASES OF ACTINOMYCOSIS COLLECTED FROM THE LITERATURE

Distribution by occupations

Butcher.....	1	Lawyer.....	2
Camp worker.....	1	Machinist.....	2
Carpenter.....	3	Merchant.....	4
Cattle dealer.....	1	Miner.....	1
Cattle raiser.....	2	Operator.....	1
Clerk.....	4	Photographer.....	1
Coachman.....	1	Physician.....	1
Conductor.....	1	Rigger.....	1
Civil service man.....	1	School boy.....	2
Dairy maid.....	1	School girl.....	4
Drover.....	1	Section hand.....	1
Factory hand.....	1	Servant.....	1
Farmer.....	16	Soda-water manufacturer.....	1
Furrier.....	1	Stableman.....	1
Housewife.....	9	Steam-boat captain.....	2
Houseworker.....	1	Stone mason.....	1
Jeweler.....	1	Teamster.....	1
Laborer.....	3	Not stated.....	42
Laundryman.....	1		

come in contact with farm life and cattle. This again raises the interesting question with regard to the mode of infection. If it is through contact with contaminated cattle, it is obvious that these men are more often exposed than any other group of persons. However, in many instances the patient had never come in contact with cattle either infected or not infected. If the infection is obtained from the bearded grasses the explanation of the predominance of the disease in farmers is obvious and of the occurrence of the disease in persons of various occupations who undoubtedly at some time in their lives come in contact with grasses. It is apparent from the long list of occupations of the patients with actinomycosis that association with the animal industry is not necessary to the infection.

It is difficult to draw conclusions concerning the distribution by states, because many factors are involved in reported cases. A patient may become infected in a different state from that in which he is resident, or the clientele of the physician who reports the case in a large measure determines the number of cases that are reported from a given state. In our series of cases most of the patients came from the middle-

west and northwest states (Table 4). These are, of course, the great cattle raising and farming states of the United States. It is interesting to note that few if any cases of actinomycosis are found among the many patients who come to us from the South and Atlantic Coast and from the far West. In the collected cases New York leads with twenty-eight of 119 cases in which the residence is stated (Table 5). Several explanations may be offered for this. New York is a city of immigrants and many of these cases may be imported. It is not always clear from the reports that the disease had been contracted in New York state. Nineteen cases of the 119 were reported from Illinois; with those from Iowa, Wisconsin, and North Dakota, all middle western states, they constitute a large percentage of the remaining cases. Fifteen cases are reported from Massachusetts. Most of these were

TABLE 4
NINETY-SIX CASES OF ACTINOMYCOSIS IN THE MAYO CLINIC
Distribution by states (United States) and provinces (Canada)

Alberta.....	7	North Dakota.....	6
Illinois.....	2	Ohio.....	2
Indiana.....	5	Oklahoma.....	1
Iowa.....	11	Ontario.....	1
Kansas.....	1	Oregon.....	1
Michigan.....	2	Saskatchewan.....	9
Minnesota.....	7	South Dakota.....	12
Missouri.....	5	Texas.....	1
Montana.....	12	Washington.....	2
Nebraska.....	4	Wisconsin.....	5

TABLE 5
ONE HUNDRED NINETEEN CASES OF ACTINOMYCOSIS COLLECTED FROM THE LITERATURE
Distributed by States (United States)

Alabama.....	1	Missouri.....	1
California.....	2	New Jersey.....	2
Colorado.....	1	New York.....	28
Illinois.....	19	North Dakota.....	6
Indiana.....	1	Ohio.....	3
Iowa.....	9	Pennsylvania.....	4
Kansas.....	1	Rhode Island.....	1
Kentucky.....	1	Tennessee.....	1
Maryland.....	6	Virginia.....	1
Massachusetts.....	15	Wisconsin.....	4
Michigan.....	1	Not stated.....	8
Minnesota.....	3		

from the Massachusetts General Hospital, in which also it is not always possible to determine where the infection was obtained. The impression is, however, that actinomycosis is far more prevalent in the middlewest and northwest states than in any other part of the United States, even making allowance for the fact that many cases diagnosed are not reported, and many cases are not diagnosed. This fact is even more forcibly brought home by an examination of the record for 1920 of the Federal Meat Inspection Commission of the United States Government (Table 6); the number of cattle retained on account of actinomycosis indicates that the disease is encountered much more commonly in the middlewest slaughter houses than in other regions of the country. Not only is this true in absolute numbers, but also relatively. Absolute conclusions cannot be drawn from this table because the source of the cattle in each instance is not known. As a general rule, however, cattle are not shipped farther than is necessary for good market conditions, and thus most of the cattle in the middlewest slaughter houses are from the middlewest, while in the slaughter houses in the south and east are

TABLE 6

ACTINOMYCOSIS IN CATTLE—FEDERAL MEAT INSPECTION REPORT, 1920

	Cattle killed.	Cattle retained for actino- mycosis.		Cattle killed.	Cattle retained for actino- mycosis.
Augusta, Ga.	5,255	0	Newark, N. J.	22,599	76
Baltimore, Md.	94,953	429	New Orleans, La.	70,923	131
Boise, Idaho.	1,902	11	New York, N. Y.	433,228	4,314
Boston, Mass.	77,346	191	Oklahoma, Okla.	264,829	1,498
Brooklyn, N. Y.	59,279	211	Omaha, Nebr.	938,147	19,271
Buffalo, N. Y.	115,609	694	Paterson, N. J.	1,605	9
Burlington, Vt.	4,194	0	Peoria, Ill.	12,638	52
Chicago, Ill.	2,155,913	40,401	Philadelphia, Pa.	104,204	263
Cincinnati, O.	181,059	1,205	Pittsburgh, Pa.	55,221	460
Cleveland, O.	128,377	513	Portland, Ore.	39,308	113
Dayton, O.	14,004	24	Richmond, Va.	9,226	33
Denver, Colo.	120,127	3,739	St. Louis, Mo.	194,039	1,475
Detroit, Mich.	70,931	421	San Diego, Calif.	9,325	648
Dubuque, Ia.	7,904	29	San Francisco, Calif. .	64,355	149
Fort Worth, Tex.	391,609	6,373	Seattle, Wash.	54,855	718
Haverhill, Mass.	1,176	0	Sioux City, Ia.	310,813	15,228
Indianapolis, Ind.	195,672	1,261	So. St. Joseph, Mo.	412,305	7,503
Jersey City, N. J.	75,292	980	So. St. Paul, Minn. .	301,958	14,883
Kansas City, Kans. .	1,214,480	30,749	Spokane, Wash.	30,598	277
Lewiston, Idaho.	1,263	13	Toledo, O.	1,985	0
Los Angeles, Calif. .	115,154	341	Washington, D. C.	13,437	19
Louisville, Ky.	15,396	58	Wheeling, W. Va.	14,058	25
Milwaukee, Wis.	106,539	460	Wichita, Kans.	18,574	931
National Yards, Ill. .	587,763	6,875	Entire Country.	9,709,819	176,456

eastern and southern cattle. Etiologically these facts may be interpreted in two ways: that the most infection among cattle results in most infection among man through direct contact, or that actinomyces is present in nature more in the west than in the east, and men and cattle are more often exposed. The result in either case would be the same.

In a letter from one of the physicians connected with a large packing plant in Chicago he states:

"It has been our observation that the so-called western grass-fed cattle from such states as Montana, New Mexico, Arizona, Texas,

TABLE 7
CASES OF ACTINOMYCOSIS IN THE MAYO CLINIC
Anatomic distribution and duration of symptoms

	Less than one month.	One to six months.	Six to twelve months.	One to five years.	Five years and more.	Unknown.	Total.
Abdominal wall.....	..	1	1	..	1	..	3
Appendix.....	..	2	3	8	1	..	14
Chest.....	..	2	..	..	..	..	2
Epigastrium (liver?).....	..	..	..	..	1	..	1
General.....	..	..	..	1	..	..	1
Head and neck.....	4	34	18	3	1	1	61
Liver.....	..	..	1	..	..	..	1
Liver and breast.....	..	..	..	1	..	..	1
Lung.....	..	..	1	..	1	..	2
Lung and neck.....	..	..	1	..	..	..	1
Mediastinum.....	..	1	..	..	..	..	1
Parotid gland and spinal cord.....	..	1	..	..	..	..	1
Scrotum.....	..	1	..	..	..	..	1
Temporal region, spinal cord, and lung.....	..	1	..	..	..	..	1
Testicle.....	..	..	1	..	..	..	1
Thigh.....	..	1	..	..	..	..	1
Tongue.....	2	1	..	..	..	..	3
Total	6	45	26	13	5	1	96

TABLE 8

ONE HUNDRED NINETEEN CASES OF ACTINOMYCOSIS COLLECTED FROM THE

LITERATURE

Anatomic location

Abdomen.....	2	Lung.....	16*
Appendix.....	7	Lung and abdomen.....	1
Arm.....	1	Lung and chest.....	1
Cecum.....	1	Mediastinum.....	1
Chest wall.....	2	Omentum and intestine.....	1
Coccyx.....	2	Ovaries.....	2
Colon.....	1	Pelvis.....	5
General.....	3	Peritoneum.....	2
Gluteal region.....	1	Ribs and vertebrae.....	1
Head and neck.....	62	Right iliac fossa.....	1
Intestine and liver.....	1	Skin.....	1
Liver.....	1	Thumb.....	1
Lumbar region.....	1	Tonsil.....	1

* Many of these are probably nocardiosis rather than actinomycosis.

Kansas, North Dakota, South Dakota, Wyoming, Utah, Colorado, and parts of Nebraska, are more frequently affected with actinomycosis than those that are fed on corn in Illinois, Wisconsin, Iowa, and Indiana. We are quite sure that this has been the experience in the packing industry in general."

This physician further suggests that it may be because range-fed cattle remain outdoors nearly the entire year, travel in herds, are wilder, and are subject to injury around the jaws in fights or by wire fences that they are more susceptible to the natural source of infection.

The distribution of the disease according to anatomic location, and to the duration of symptoms in the cases in the Mayo Clinic is shown in Table 7. From this it will be seen that lesions in the head and neck occur nearly twice as often as in other parts of the body. Next in number are the cases of the appendix and cecum. However, almost any part of the body may be involved. In general the same may be said concerning the cases collected from the literature (Table 8). The conclusion is inevitable that the alimentary tract plays a very important part in the source of infection. This is striking in the details of the case histories in almost all of which dental or tonsillar trouble immediately preceding the onset of the disease is mentioned. Immediately following extraction of a tooth the lesion appears in the region of the jaw or submaxillary gland. The duration of symptoms

before the patient presents himself is, contrary to the usually accepted idea, rather short. In six cases of our ninety-six the history was under one month; in two of these only ten days had elapsed after choking over a barley beard before the lesion appeared. Practically all patients with lesions of the head and neck presented themselves within twelve months and most of them within six months. The period of symptoms was practically the same in the other cases. However, the majority of the patients with actinomycosis of the cecum and appendix presented themselves after from one to five years. Evidently the disease is usually acute or subacute, except in the cecum and appendix, where it is chronic. The incubation period is very difficult to determine because it is almost impossible to obtain a history of definite injury or inoculation.

In conclusion we wish to emphasize that actinomycosis, while an uncommon disease, is not so rare as many imagine. In a patient with an acute or subacute infection of the cervicofacial region, especially if there has been dental trouble on the affected side, or a history of definite injury, this disease must be suspected. A differential diagnosis must also be made in those types of abdominal lesions in which a sinus persists after drainage of an abscess. The careful examination of the discharge in either type of case for characteristic sulphur bodies will lead to the correct diagnosis clinically, which is readily substantiated by simple laboratory procedures.

While the biologic characteristics of the causative organism and its place in the vegetable world have been defined, the etiologic factors concerned in the production of infection in man or beast are not known. It is, therefore, still of interest to report accurately all details regarding cases of actinomycosis and thus stimulate further research in the life-history of actinomyces.

NOTE: The Bibliography is on page 1088.

ACTINOMYCOSIS OF THE TONGUE*

GORDON B. NEW AND FRED A. FIGI

Actinomycosis rarely occurs primarily in the tongue. It may occur in this location by metastasis or by direct extension from involved contiguous structures. Illich, in 1892, found only fifteen in 569 cases in which the growth originated in the tongue. Ruhräh, in 1899, collected 1094 cases of actinomycosis in the literature. Krymow, ten years later, was able to find only twenty-seven cases in which the tongue was primarily involved. von Baracz reported three of this type in a series of fifty-two cases of infections in the head and neck. Schlange reported only one such case in a total of sixty general infections.

Undoubtedly the tongue is more often involved than these data indicate. Three cases have been seen in the Mayo Clinic since October, 1919; none had been recorded previous to that time, and thorough microscopic examination of all specimens of inflammatory tumors of the tongue in the Mayo Clinic museum did not reveal another case. Such examination is not necessarily final, since it was not possible to study the pus contained within the nodules. Four hundred thirty-seven tumors of the tongue, of all types, have been examined in the Mayo Clinic. Of these, 300 were malignant, 100 benign, and thirty-seven inflammatory, so that the three cases of actinomycosis of the tongue formed 0.7 per cent of the entire number.

The actinomycotic or so-called wooden-tongue of cattle is of comparatively frequent occurrence. Claus estimates the incidence of this type of lesion as 29 per cent of all actinomycotic infections in cattle, and Leclerc as 18 per cent. von Hollandt notes that in at least 5 per cent of the tongues of slaughtered hogs definite, encapsulated, actinomycotic nodules can be demonstrated. The rarity of the infection of this organ in man has been explained by Poncet and Berard as owing to the fact that the tongue consists of muscle-bundles richly supplied with blood vessels and protected with a thick epithelial covering. Since the structure of this organ in animals is practically the same as

* Introduction omitted; published in full in the American Journal Medical Sciences, 1922, clxiii, 507-516. Copyright, Lea & Febiger, Philadelphia.

in man the explanation is hardly sufficient. It seems more logical to attribute the relatively more frequent occurrence in animals to the fact that their habits and mode of life bring them in more direct contact with infectious material. It is conceded that most infections due to actinomyces are of vegetable origin, such as the various grasses and grains; barley beards are supposedly the most common cause. von Hofman and Bostroem have shown that the ray fungus is an almost constant finding on the grain beards in the tonsillar crypts of slaughtered hogs. von Hollandt, who has conducted an excellent investigation in the slaughter houses of Dresden to ascertain the frequency of infection of the tongue in supposedly healthy hogs, states that at least 73 per cent are due to infected plant particles.

Bostroem, who studied serial sections of primary actinomycotic tongues of cattle, was able to demonstrate foreign bodies in nearly all recent cases. The presence of such foreign bodies has also been shown in the primary lingual nodules in man by Fischer, Jurinka, von Baracz, Harms, and Kockel. It is readily understood how these spore-bearing particles, when thrust through the mucous membrane of the tongue, can find a favorable medium in which the anaërobic fungus may proliferate. That foreign bodies are not the only source of infection is quite evident, however, since the fungus has been demonstrated in a number of instances in the cavities of carious teeth in healthy persons, and trauma to the organ by such teeth with subsequent infection is highly probable.

In reviewing the literature we found records of thirty-five cases of primary actinomycosis of the tongue; our three cases make a total of thirty-eight. Twenty-seven of the series were in males and ten were in females. The disease occurs in adults; only one case has been reported in a patient under twenty, a young man of eighteen.

Incidence of the disease by decades according to ages recorded:

Age.	Cases.
18.....	1
21 to 30.....	8
31 to 40.....	6
41 to 50.....	9
51 to 60.....	5
61 and over.....	4

The condition is more commonly found in farmers, or in persons whose rural life exposes them to infection. The disease cannot be said

to be occupational, since, besides farmers and their coworkers, a physician, an office girl, a janitor, a cabinet maker, two merchants, a naval pensioner, a stone mason, and a judge are noted in the series. One of the patients seen in the Clinic, a judge, mentioned a habit of chewing bits of grass while he played golf. The occupation of twenty-eight patients was recorded. Fifteen (53 per cent) were connected with rural life, thirteen (46 per cent) were patients not connected with rural life.

The clinical history of actinomycosis of the tongue varies in different cases. The patient usually has a single, isolated nodule in the anterior half of the tongue, often near the tip, varying from 1 to 1.5 cm. in diameter. This location is significant, since in giving a history the patient often mentions injury to the tongue by the teeth, or some foreign body. The condition may be acute in onset, with severe pain, throbbing, local tenderness, general malaise, and an elevation of temperature, as in abscess of the tongue. It may develop insidiously during the course of several months, or even three or four years. Without secondary infection the process is usually slow to develop. Enlargement of the regional lymph nodes has often been observed, but only staphylococci, never actinomyces, have been found in these, and the adenitis subsides with the clearing of the local condition of the tongue.

DIAGNOSIS

The diagnosis must be based on the clinical picture and confirmed by microscopic examination. Aspiration of the contents of the suppurating nodule is usually unsatisfactory; it is best to excise the entire nodule for diagnosis. Often only a few of the characteristic granules necessary for a positive diagnosis may be present within the nodule, and unless these granules are secured in the small specimen removed for microscopic examination, it is impossible to make a diagnosis. Grossly the lesion must be distinguished from tertiary syphilis, tuberculosis, epithelioma, inflammatory cyst, and fibroma. One of our patients was referred with a diagnosis of probable malignancy. One patient was believed to have an inflammatory nodule and the third a simple infected cyst.

PATHOLOGY

A small isolated nodule, varying in size from 0.6 to 3 cm., and enclosed in a fibrous capsule, will usually be found near the dorsum, unless the entire thickness of the tongue is involved. The nodule often

becomes infected secondarily with the formation of a small encapsulated abscess. This may rupture spontaneously or, in rare instances, a diffuse lingual abscess may form. Baracz's third case was of the latter type.

The overlying mucous membrane varies in appearance with the stage of the process and consequently may be normal, yellowish, or elevated and tense, as though covering a superficial cyst or a small abscess about to rupture. It rarely ulcerates. Some writers mention a peculiar bluish-red discoloration as decidedly suggestive of actinomycosis in this location, but this was not seen in our cases. The usual picture of a diffuse, indefinitely outlined induration with multiple sinuses, which depend on the ramifying granulation tissue tracts extending into the adjacent normal tissue, is rarely seen in the tongue; it was seen in only one case in the series, that of Fischer.

Most observers agree that no suppurative process is characteristic of actinomycosis, and that suppuration is always the result of secondary infection usually due to the staphylococcus.

TREATMENT

The condition is treated medically and surgically. Arsenic has been used and believed to be of some therapeutic value, but its action is probably due to its systemic effect. Injections into the tongue of various antiseptics and germicides, such as bichlorid of mercury, tincture of iodin, and zinc chlorid, have been made with definite improvement, but such methods seem hazardous. The nodules have been known to disappear by the use of large doses of potassium iodid internally (Claisse). Poncet and Berard, however, concluded that incision or spontaneous rupture of the abscess in conjunction with the potassium iodid internally produced much more rapid and satisfactory results. Surgical treatment alone, or combined with the medical treatment, seems to be the rational procedure. Wide excision with primary suture of the wound was done in our cases, and is the treatment of choice if a discrete, isolated nodule is present. If the abscess is too large for excision, drainage with or without curettement is advisable. Daily swabbing of the wound with tincture of iodin, packing with iodoform gauze, the administration of large doses of potassium iodid, and the use of radium as employed in the Mayo Clinic in all cases of actinomycosis of the head and neck, are unquestionably of distinct benefit.

PROGNOSIS

The prognosis varies with the stage of the process and the clinical picture at the time of the patient's examination. It is favorable in those cases in which a small nodule is situated well forward near the tip of the tongue; less favorable in those in which there is a diffuse area, especially if it is near the base of the tongue, or if there is a definite abscess.

Death has been reported in one case (Mayer's) from multiple abscesses around the lower jaw, neck, and upper chest one and one-half years after excision of the primary nodule near the tip of the tongue. The abscesses were probably due to metastasis from the primary focus.

CASE REPORTS

Case 1 (A292538). Mrs. S., aged sixty-three years, wife of an implement dealer, came to the Clinic October 9, 1919, because of a small nodule on the tip of the tongue which had been present for two months. The nodule had been incised by her home physician one week before, and a small amount of pus evacuated.

Examination showed a small, hard, whitish nodule about 0.63 cm. in diameter on the dorsum of the tongue just back of the tip. Slight induration extended down into the tongue. The nodule was excised under local anesthesia and on microscopic examination was shown to be actinomycosis. Fourteen months later there was no recurrence.

Case 2 (A265308). Judge F., aged fifty years, came to the Clinic September 17, 1920, complaining of a small nodule in his tongue. Four weeks before he had noticed a burning sensation on the dorsum of the tongue, which he thought was due to heavy pipe smoking. Five days before coming to the Clinic he discovered a small nodule in his tongue. He consulted two physicians, who thought that it was probably malignant.

Examination revealed an indurated nodule, only slightly tender and freely movable, 1.25 cm. in diameter, just to the right of the midline of the dorsum of the tongue, and about 3.75 cm. back of the tip. The nodule was believed to be inflammatory, and excision for definite diagnosis was recommended. Actinomycosis was diagnosed. The patient was given large doses of potassium iodid. He has not had a recurrence.

Case 3 (A339709). Mr. M., aged forty-six years, a meat cutter, was examined in the Clinic November 3, 1920. He complained of many symptoms, most of which were apparently functional, following the nervous shock incident to the death of his son seven years before. He was referred to the Section on Laryngology, Oral and Plastic Surgery, for examination because of a small nodule on his tongue which had appeared a week or ten days before.

On examination a slightly tender, fluctuant nodule about 1.25 cm. in diameter was found on the left side of the dorsum of the tongue. The mucous membrane covering the nodule was slightly elevated and yellowish. A diagnosis of infected cyst was made, and the lesion excised under local anesthesia. Microscopic examination showed the condition to be actinomycosis. The patient was given large doses of potassium iodid.

NOTE: The Bibliography is on page 1088.

TABULATED DATA OF THE CASES

No.	Author, date.	Sex, age.	Occupation.	Etiologic factors.	Location of lesion. Symptoms. Duration.	Diagnosis.		Operative findings. Treatment.	Result.
						Clin- ical.	Micro- scopic.		
1	Hacker, 1885	M. 30		Patient had opened "ac- tino" abscess on jaw of cow two months before.	Tip.	+	..	Excision.	
2	Hochenegg, 1886	M.	"Son of farmer."	Accustomed to chewing grain during harvest.	Right anterior quadrant.	+	..	Incision and curettement (rapid local healing).	Death from mul- tiple abscesses of jaws, neck, and chest 1½ years later.
3	Mayer, 1887	M.	Farm hand.		Middle, near tip.	+	..	Excision; suture.	?
4	Santer, 1888	M. 50				+	..	Excision; suture.	No recurrence.
5	Santer, 1888	M. 50	Gentleman farmer.		Right anterior quadrant, 1 week.	+	..	Nodule size of "hazelnut." Mu- cous membrane violet. Exci- sion; sutured.	No recurrence.
6	Ullmann, 1888	F. 56	Wife of field worker.		Dorsum 1 cm. from tip.	+	..	Hard nodule size of "grape." Mucosa normal. Primary liga- tion lingual artery. Excision of one-half of tongue.	No recurrence.
7	Ullman, 1888	M. 54	Farmer.		Right anterior quadrant, 4 weeks.	+	..	Softened area in middle of tongue. Drainage of abscess; excision of walls; suture.	No recurrence.
8	Maydl, 1889	M. 48	Physician.	Moistened finger with tongue while inspecting meat.	Middle, 3 cm. from tip. Pain. Patient sick 2 months.	+	..	Hard nodule size of "cherry." Excision; suture.	Recurrence. No recurrence.
9	Kubecki, 1889	M. 55	Farmer.		Right anterior quadrant. Pain 14 days.	+	..	Nodule size of "hen's egg." In- cision twice. Recurrence 4 months later. Drainage; cu- rettement.	No recurrence.
10	Zuhra, 1889	M. 56	Forester.		Recurrence right anterior quadrant, 3 or 4 weeks. Recurrence after 4 months.	+	..	Incision.	No recurrence.
11	Zuhra, ...	F, old			1 week.	+	..		

TABULATED DATA OF THE CASES—Continued

12	Schartau, 1890	M. 24	Field worker.	Rye beard in tongue while threshing.	Right anterior quadrant, 14 days.	..	+	Nodule size of "pea." Grain covered with actinomyces. Incision; curettement.	No recurrence.
13	Baracs, 1890	F. 23	Office girl.		Left tip. Patient sick 3 months.	..	+	Round, "pea." Incision; curettement.	No recurrence.
14	Fischer, 1890	M. 20	Field worker.	Barley beard in tongue while threshing.	8 days.	..	+	Soft, fluctuant nodule size "small nut." Grain beard with fungi growing about it. Incision; curettement.	
15	Illich, 1892	M. 75	Janitor.		Dorsum 1 cm. from tip. Sick 2 months.	+	..	Hard nodule size of "1/4 hazelnut." Mucosa normal. Incision.	No recurrence.
16	Illich, 1892	M. 36	Cabinet maker.	Soreness caused by pipe stem often noticed.	Right half. Soreness 3 weeks.	+	..	Hard nodule. Incision. curettement.	No recurrence.
17	Schlange, 1892	..			Middle of dorsum.	?	..	Firm nodule size of "hazelnut," resembling gummas. Incision; curettement.	No recurrence.
18	Jurinka, 1895	M. 46	Merchant.	Accustomed to chewing grain.	Left half. Pain. Tenderness. Induration for 3 months ascribed to sting noted 2 years previously.	..	+	Nodule size of "cherry." Cavity 3 mm. in diameter in center containing five "actino" granules around a grain beard. Incision; curettement.	
19	Frey, 1897	F. 28			Midline of dorsum; region of circumvallate papillae and forward. Pain; 4 years.	+	..	Tenderness. Nodule size of "cherry." Swelling in middle of tongue 3 cm. in diameter, covered with papillary growths. Pus and granules. Incision.	Outcome uncertain.
20	Frey, 1897	M. old	Fruit merchant.	Tongue injured by fruit stone 3 weeks before.	Left, anterior quadrant. Pain.	+	..	Hard nodule size of "nut." Excision (local anesthetic).	No recurrence.
21	Claiss, 1897	M. 39		Irritation from jagged, carious tooth produced ulceration.	Right margin anteriorly. Ulceration healed following extraction of tooth. Nodule 3 months later. Abscess several months later.	..	+	Ulceration primarily a fluctuant nodule as recurrence. Actinomyces granule obtained on aspiration. Process cleared under potassium iodid.	No recurrence.
22	Cooper, 1899	M. 60	Naval pensioner.	Habit of chewing straw.	Midline of dorsum; 1 in. from tip.	..	..	Nodule size and shape of almond. Lesion thought to be malignant. Abscess 1/4 in. in diameter. Granules. Excision of tongue.	No recurrence.

TABULATED DATA OF THE CASES—Continued

No.	Author, date.	Sex, age.	Occupation.	Etiologic factors.	Location of lesion. Symptoms. Duration.	Diagnosis.		Operative findings. Treatment.	Result.
						Clinical.	Microscopic.		
23	Rigler, 1901	M. 45	Farmer.		Left side. Pain. Abrupt onset. Abscess developed and ruptured in 3 days. Recurrences 4 years later and 4 years and 7 months later.	..	+	Marked swelling. Single abscess primarily. Multiple abscesses as recurrence. Actinomyces found on second recurrence. Incision.	
24	Smirnow, 1901	F. 60	Farmer's wife.	Sheared sheep having actinomycosis	7 months.	..	+	Hard nodule size of "hazel nut." Potassium iodid for 23 days without result. Excision.	
25	Baracz, 1902	F. 32	Farmer's wife.	Chewed wheat while threshing.	Right posterior quadrant, 3 weeks.	..	+	Hard nodule size of "nut." Grain beard. Incision; curettement.	No recurrence.
26	Baracz, 1902	M. 36	Farmer.		Dysphagia. Pain 1 week; recurrence 3 months later.	..	+	Diffuse swelling. Tongue twice normal size; fluctuant area. Foreign body, pus with granules. Incision.	One recurrence. Patient lost sight of.
27	Kellock, 1902	M. 18	Stone mason.		Right dorsum and margin. Noticed for 2 days.	..		Soft swelling size of "pea." Numerous granules. Incision and curettement. Potassium iodid internally.	Apparently no recurrence.
28	Schwiehorst, 1903	M. 27	Day laborer.		Middle. Dysphagia. Pain 6 weeks.	..	+	Nodule. No fluctuation. No foreign body. Diagnosis by aspiration. Incision; curettement.	No recurrence.
29	Juffinger, 1903	F. 34		Sensation as of fishbone thrust into tongue while eating 5 weeks before.	Right margin opposite first molar. Dysphagia. Pain; 5 or 6 weeks.	..	+	Hard, red nodule 0.2 by 1.5 cm. with small abscess. Pus with granules.	
30	Maier, 1906	M. 73			Right half; 6 weeks.	..	+	Swelling. Pus with granules. Excision under local anesthesia.	No recurrence.
31	Krynnow, 1908	M. 48	Farmer.		Left anterior quadrant. Swelling. Pain; 6 weeks.	..	+	Fluctuant nodule 2 cm. in diameter. Pus with granules. Incision and curettement.	
32	Krynnow, 1908	M. 42	Artillerist.		Right margin opposite inferior third molar. Abscess ruptured in 20 days. Nodule appeared later.	..	+	Hard nodule 1.5 cm. in diameter with fistulous opening in center. Pus with granules. Excision under chloroform.	No recurrence.

TABULATED DATA OF THE CASES—Concluded

33	Roth, 1916	F. 22	Wife of rancher.	500 cattle graze near house during summer.	Right anterior quadrant. Tenderness; 4 weeks.	..	..	Recurring pustules with coales- cence and ulceration. Scrap- ings and culture showed actino- myces. Removal of one-third of tongue and cauterization of area.	No recurrence.
34	Harms, 1920	F. 65			Dorsum near tip, 0.5 cm. from margin. Tender- ness. Pain, 14 days.	..	+	Hard nodule size of "hazelnut." Foreign body in center of ab- scess. "Splinter of wood?" "Grain beard?" Excision with V.	No recurrence.
35	Kockel, 1920	M. 40		Habit of chewing tooth- picks.	Tenderness. Pain; 14 days.	..	+	Abscess size of "pea" in center of inflammatory mass. Small splinter of wood in abscess.	No recurrence.
36	New,	F. 63	Wife of imple- ment dealer.		Dorsum, just back tip. Itching sensation; 2 months.	..	+	Hard, whitish nodule 0.62 cm. in diameter. Actinomycosis. Excision under local anesthesia.	No recurrence.
37	New,	M. 50	Judge.	Habit of chewing grass while playing golf.	Left dorsum, middle third. Burning; 5 weeks.	..	+	Indurated nodule 1.87 cm. in diameter. Actinomycosis. Ex- cision under local anesthesia.	No recurrence.
38	New,	M. 46	Meat cutter.		Middle, just to right of midline. Slight tender- ness; 10 days.	..	+	Soft, fluctuant nodule 0.62 cm. in diameter. Actinomycosis. Excision under local anesthesia.	No recurrence.

ACTINOMYCOSIS OF THE CENTRAL NERVOUS SYSTEM*

FREDERICK P. MOERSCH

It is difficult to determine the frequency with which the central nervous system is involved in cases of actinomycosis. Osler reports three cases. The same cases are referred to by Lewandowsky, Oppenheim, and others, each author in turn calling attention to the rarity of the disturbance. Von Langenbeck and Kiel, in 1845, reported the first case of involvement of the central nervous system, but it was not recognized as such at the time. Ponfick, in 1882, reported two cases of actinomycosis of the brain. At necropsy in one case two foci were found in the occipital lobe; in the other the process had extended through the sphenoid bone into the frontal and temporal lobes.

Bollinger, in 1887, reported the first case of primary actinomycosis of the brain, and recently Fontecilla has reported a case of compression myelitis subsequent to vertebral actinomycosis. Sagredo, in 1919, collected twenty cases from the literature of actinomycosis of the central nervous system. In none of Ruhräh's cases collected in this country was the central nervous system involved. Baracz, in 1903, reported sixty cases, and Cranwell, in an exhaustive investigation in South America, did not find cases in which the central nervous system was involved.

Howard, in 1903, collected eighteen cases with involvement of the central nervous system, thirteen secondary, and five primary. Sagredo's are included in the forty-eight cases of actinomycosis with central nervous system involvement which the writer has collected.

In this group of forty-eight cases, males were more frequently affected than females. The average age of patients was about thirty years. The duration of the disease ranged from six months to three years, rarely more than one year. The majority of cases followed actinomycosis of the jaw, the central nervous system being involved by contiguity. The disease may occur primarily in the brain, as was

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the case in Bollinger's patient; this, however, is unusual. Meningeal involvement is the usual form of central nervous system affection. Abscess formation is fairly common, while tumor formation is rare. Involvement by way of the lymphatics has never been noted.

Musser and his colleagues, Sagredo, Corinth, Howard, and others, have reported results of analyses of the spinal fluid in the cases observed by them. Musser found in one case a turbid spinal fluid, Sagredo obtained 70 per cent polymorphonuclears and 30 per cent lymphocytes, while Corinth reports the finding of purulent fluid containing streptococci. No mention is made of the early findings or of time at which the purulent fluid developed.

Headaches played but a slight part in the early symptomatology of the disease, although in several cases marked neuralgic pains over the swelling, especially when it was around the face, were noted. Convulsive attacks or palsies were not uncommon, but presented nothing of diagnostic value in the progress of the disease. As a rule, the disease had developed to a marked degree before the diagnosis was made. In several cases the diagnosis was not suspected ante mortem; only after finding sulphur granules postmortem could a diagnosis be made. In spite of the severe infection, the temperature was usually low and rarely was any septic rise noted. The afebrile course of the disease was noted as early as 1887 by Bollinger.

SEVENTY-FOUR CASES OF ACTINOMYCOSIS IN THE MAYO CLINIC

The cases, reviewed for this study, were observed in the Mayo Clinic. In all of the seventy-four cases a positive diagnosis was made microscopically by finding the typical sulphur granules in the pus. Eighty per cent of the patients were males; the greater number were young adults. The youngest patient was fifteen, the oldest seventy-one. The large percentage were farmers, or were in some way connected with rural life. Direct exposure to diseased cattle could rarely be determined.

The primary location, so far as could be determined, was facio-cervical in fifty-four patients, abdominal in sixteen, pulmonary in three, and cutaneous in one patient.

Twenty-six patients are known to be living, thirty cannot be traced, and eighteen are dead. Of the twenty-six patients who are living, the majority have fully recovered and have been well for from five months to three years. The location of the actinomycosis in the eighteen

patients who died with the disease was abdominal in eight, faciocervical in five, pulmonary in three, and abdominopulmonary in two.

There was positive evidence of central nervous system involvement in five of the eighteen patients who died of actinomycosis; the evidence was confirmed by necropsy in two. Two patients with signs of involvement of the central nervous system are alive (Cases 4 and 7, Table 1). Two other patients had signs of central nervous system involvement, but the subsequent course is not known. These two patients are not included in the series. Undoubtedly other cases of the series of seventy-four had central nervous system involvement, but unfortunately the cause of death could not be determined. The two patients who died present fairly typical pictures. The histories are reported herewith:

Case 1 (A254829). A man, aged forty-one years, was admitted to the Clinic January 3, 1919. His personal history was negative, except for tonsillitis in August, 1918, when he had first noticed that it was becoming increasingly difficult to open his mouth. He complained only of pain in the right temporal region, most severe at night.

Examination revealed ankylosis of the jaw, deafness of the right ear, which came on with tonsillitis, and an unerupted upper right third molar. The neurologic examination was negative. An indeterminate diagnosis was made and January 8, 1919, roentgen-ray treatments not having caused any apparent change, the jaw was stretched and the upper third molar extracted.

The swelling in the region of the right parotid increased gradually and, February 24, a phlegmon over the angle of the jaw was drained. The condition spread and not until one month later, when a phlegmon in the right cervical region was drained and sulphur granules discovered in the pus, was the diagnosis of actinomycosis made.

The patient gradually became weaker; no benefit had been experienced from radium treatment. A second neurologic examination, April 8, showed paralysis of the right external rectus, nystagmus to the right, impairment of pain and touch over the right fifth nerve, with weakness of the masseters, temporal, and pterygoid muscles. All deep reflexes were exaggerated, Kernig positive, plantar reflexes flexor. The neck was rigid. The mental state was unimpaired. A diagnosis of low grade meningitis was made. Spinal puncture showed a cloudy, thick, purulent fluid; the cells were not counted, but pus cells predominated. No organisms were found; no actinomycetes or sulphur granules. The neck gradually became stiffer; the knee jerks were difficult to obtain. The right seventh nerve also showed considerable weakness. The patient died April 22, 1919, after being prostrated and semiconscious for two days.

Necropsy revealed an extensive actinomycetic granuloma of the right parotid region with erosion of the right petrous portion of the temporal bone and basilar and spinal leptomeningitis. The exudate was yellow. A definite sinus could be seen from the parotid region burrowing through the thick portion of the temporal bone into the middle cerebral fossa. Cultures from the spinal fluid gave short chain streptococci, but no ray fungi.

Sections were taken from representative areas of the brain and cervical cord and stained with hematoxylin-eosin, thinin, Cajal's, and Gram's stains. In sections from the dorsal surface of the brain moderate lymphocytic infiltration of the pia occurred

The cortex did not show marked change and there was no blood vessel infiltration. Gram's stain was negative for this region. In sections from the basal portions of the brain, extensive infiltration of the meninges, chiefly mononuclear in character, was seen. The process was confined almost entirely to the membranes, the cortical substance remaining relatively free. In sections from the right pons (Fig. 345) a typical ray fungus growth with marked polymorphonuclear infiltration was found in the membranes. Gram's stain in every case appeared to be elective, and often the growth might have been overlooked if only the usual stains had been employed. Sections of the cord showed similar infiltration of the membranes, predominantly lymphocytic, but no ray fungus.

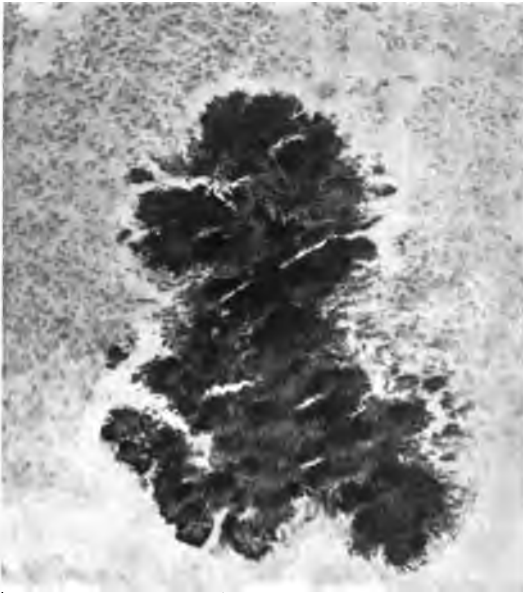


FIG. 345 (Case A254829).—Ray-fungus in the right pontile region. (Gram's stain.)

Case 2 (A326059). A man, aged twenty-five years, a farmer, was examined September 11, 1920. In February, 1920, he had noticed slight drooping of the right eyelid, with ringing and deafness in the right ear. Some time prior to this he had sustained a small cut over the right eye by a whip. Two weeks later burning pain and numbness in the right leg made walking difficult. About June 1, 1920, he began to experience pain in the right frontal and temporal regions, with swelling in the temporal area.

Examination, July 28, revealed swelling of the right temporal region with exophthalmos of the right eye. The patient was somewhat emaciated. The neurologic examination showed blurring of both fundi, deafness in the right ear, diminution of sensation over the supra-orbital region, and slight weakness of the right leg. July 31, pus containing actinomycetes was drained from a small abscess over the upper right lid. The spinal fluid report at this time was: Nonne positive; 1,889 polymorphonuclear leukocytes, 587 small lymphocytes, and Lange's test 0111221000. Because of the headache and blurring discs a decompression operation was performed August 10. The findings were negative.

The patient was dismissed from observation and returned September, 1920, when the spinal fluid showed polymorphonuclears 841, lymphocytes 128, and no granules; his temperature was 100; he had no clinical signs of meningitis. He gradually became worse; emaciation was marked; he passed into a mild state of confusion with muttering delirium.

September 26, the patellar and Achilles' reflexes could not be obtained, Babinski's reflex was absent, and there was only moderate rigidity of the neck. Until the day of death no paralysis occurred, although the right leg was weak. At times the headache was so severe that the patient walked around for relief. He died September 28, 1920.

Necropsy revealed the scar of a previous operation, but no infection or growth. The membranes were adherent at the right orbital ridge and a thick layer of gelatinous, green-



FIG. 346 (Case A326059).—Ray-fungus and exudate in the cerebellopontile region. (Gram's stain.)

ish yellow pus surrounded the area and covered the entire basal surface. Throughout the pus numerous pin point granules could be seen. The point of infection was apparently at the orbital ridge, where a spot the size of a pencil head could be distinguished, from which a sinus led directly into the orbital space where the pus was very thick and tenacious. The entire cord was bathed in a thick, greenish yellow pus, most marked in the caudal region where it was especially abundant.

Sections were taken from representative areas of the brain and cord and stained with hematoxylin-eosin, thionin, Cajal's, Weigert's, and Gram's stains. As in Case 1, the convolutions showed but slight involvement. Sections from the base and especially those taken at the cerebellopontile angle showed severe meningeal infiltration and some polymorphonuclear cells. The reaction was confined chiefly to the membranes where the

fungus was present, although the brain substance showed some cell degeneration and very slight blood vessel infiltration (Fig. 346).

Sections from the cord showed a severe meningitis, with many polymorphonuclear cells. The central canal throughout was filled with polymorphonuclear cells; the exact cause of their occurrence remains uncertain (Fig. 347). The cord substance showed some swelling of the nerve cells with displaced nuclei and a moderate blood vessel infiltration, but no abscesses or foci were discovered and no fungi were found in the membranes of the cord.



FIG. 347 (Case A326059).—Section of the spinal cord showing marked meningitis with ependymitis.

What has been said of actinomycosis apparently holds true for many other mycotic affections. Ophüls, in 1905, reported thirteen cases of coccidroidal granuloma, three of which showed central nervous system involvement. Rusk and Farnell reported several cases of oidiomycosis with meningitis. Since the work of Gilchrist over twenty cases of blastomycosis with nervous system involvement have been reported. Bassoe, in 1906, first reported a case of blastomycosis with cerebral involvement. Montgomery, in 1917, in a review of blastomycotic infections reported eight cases with brain abscess and several others with involvement of the cord and meninges.

CONCLUSIONS

Actinomycotic involvement of the central nervous system is not rare. The disease process is usually secondary to some other focus in the body, and apparently the meningeal type, in which the infection takes place by contiguity, is most frequent. The course of the disease is chronic, with markedly insidious onset; meningeal involvement occurs without any clinical signs or symptoms. There is some evidence that involvement of the meninges occurs long before the spinal fluid shows evidence of trouble, but the serologic examination usually shows a pleocytosis long before there is any clinical evidence of meningitis. It has been suggested that clinical signs of meningitis develop only after secondary infection has occurred. The positive spinal fluid with but slight signs of meningitis is almost pathognomonic. In no other form of severe meningitis do we see such a lack of clinical findings. The ability of these patients to be up and about, presenting but few complaints, as moderate headache, slight rigidity of the neck, and only slight temperature, is practically unknown among other forms of meningitis. During the terminal stage of actinomycosis, with the onset of palsy, and so forth, the diagnosis is certain, but in the early stages a positive diagnosis on clinical findings alone is practically impossible.

The presence of a chronic phlegmon of the head or neck should indicate the possibility of actinomycosis and an examination of the spinal fluid and a search for sulphur granules should be made.

The course of the disease is characterized by low grade fever, rarely more than 101, not of the usual septic type, headaches are common and chronic, but not unusually severe, terminal delirium, and profound emaciation.

The importance of an early diagnosis in actinomycosis is paramount because of the prognosis. Involvement of the nervous system makes prognosis hopeless. Potassium iodid, salvarsan, and so forth, have been tried, but with uniform failure.

TABLE
ACTINOMYCOSIS OF THE CENTRAL NERVOUS SYSTEM—SEVEN CASES

Case.	Sex. Age.	Occupation.	Primary focus.	Duration of symptoms, months.	Neurologic signs of central nervous system involvement.	Headache.	Temperature.	Mental symptoms.	Lymphocytes.	Spinal fluid.	Diagnosis.	Remarks.
A130341	M. 34	Farmer.	Chest.	18	General weakness, tremor, and increased reflexes; repeated convulsive attacks.	Moderate.	99?	Terminal mental apathy.	11,000 16,000	Negative.	Actinomycosis, probably abscess.	Patient died at home; no necropsy.
A254829	M. 41	Farmer.	Jaw.	9	Cranial nerve palsy, choked discs, increased deep reflexes, rigid neck, and Kernig's sign positive.	Moderate.	99 100	Terminal unconsciousness.	6,800 15,000	Purulent.	Actinomycosis, meningitis.	Necropsy showed meningitis of both brain and cord.
A320685	M. 38	Farmer.	Jaw.	8	Cranial nerve palsy, rigid neck, and patheticus.	Severe, localized in left frontal to parietal areas.	Moderate.	Mild delirium.	9,000 11,800	Nonne + Polymorphonuclears 1735. Lymphocytes 170.	Actinomycosis, meningitis.	Patient died at home; no necropsy.
A325362	M. 20	Farmer.	Jaw.	?	Proptosis, cranial nerve palsy, rigid neck. No clinical signs of meningitis.	Moderate.			6,800	Negative.	Probably actinomycosis, meningitis.	Patient alive.
A326059	M. 23	Farmer.	Jaw.	8	Cranial nerve palsy, headache, rigid neck, delirium and numbness in limbs.	Severe, localized in temporal area.	98 100	Mild delirium.	6,900	Nonne +. Lange 011221000. Polymorphonuclears 1889. Lymphocytes 587.	Actinomycosis, meningitis.	Necropsy showed meningitis of both brain and cord.
A347777	M. 24	Farmer.	Jaw.	7	Cranial nerve palsy, rigid neck, mental torpor.	Moderate.	99 100	Mild grade delirium.	12,000	Negative.	Actinomycosis, meningitis.	Patient died; no necropsy.
A371666	F. 27	Housewife.	Jaw.	6	Motor and sensory involvement of right fifth nerve and headache. No clinical signs of meningitis.	Moderate.	99 101		11,000	Wassermann +. Nonne +. Polymorphonuclears 92. Lymphocytes 400.	Actinomycosis, meningitis.	Patient alive.

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THE RÔLE AND DEVELOPMENT OF DRUG THERAPY*

LEONARD G. ROWNTREE

In this symposium we are attempting to determine the value of drugs in treatment. The degree of success which we will attain obviously depends on the wisdom shown in the selection of men to represent these various fields of practice. Needless to say only those most eminently fitted to pass on these matters have been chosen.

Before entering on more detailed considerations, a few moments might be spent to advantage in a general survey of treatment as it exists today and in a consideration of the more important factors which have in the past or may in the future exercise a retarding or accelerating influence on the progress of treatment.

In considering the rôle of drugs in medicine perspective is essential. Medical interests have become specialized to such an extent that the broad point of view is the exception. At times the sick succumb to a conflict of special interests, as well as to disease. Practice is complex and each field so intricate that the specialist seeing through his own glasses centers only on part of the picture and loses sight of the patient as a whole. For true perspective we must return to Hippocrates. The father of medicine practiced prevention and cure. He was a general man. His therapeutic platform comprised several planks, among them surgery, drugs, dietary régime, physical and psychical therapy. Recognizing the limitations of his day he sought to assist nature the "*Vis medicatrix naturæ*" and through the control of the vital functions of the body to promote the natural processes of repair, thereby compelling the patient himself to participate in the cure. He kept two objects in mind, to do good or at least to do no harm. Since his day medicine has progressed, but his point of view has not been superseded.

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PREVENTIVE MEDICINE

The achievements of preventive medicine have stirred the admiration of physicians and surgeons alike. From the laying down of the laws by Moses sanitation has made great progress, but since the days of Pasteur this has been unprecedented. Within the past three centuries the average working life of English speaking man has been doubled. By the public health service we are protected both from within and from without. Vigilance exercised at our ports protects us from foreign born infections and sanitation throughout the land is decimating many of our endemic diseases. So far as America and western Europe are concerned preventive medicine is responsible for the greatest medical triumphs of all time.

CURATIVE MEDICINE

In the field of treatment come medicine, surgery, and the various specialties. This division is logical and counts for efficiency provided that the specialism does not result in loss of vision. Surgery has made almost unbelievable progress during the last century, particularly in the latter half. Many conditions formerly considered medical admittedly fare better now under surgical treatment. Although surgical technic has improved enormously the greatest success of surgery rests on the use of drugs. Anesthesia, antisepsis, and asepsis have made possible the achievements of surgery.

With regard to surgery it is important to recall that it is but one form of therapy and that medical treatment applied simultaneously is often of the greatest consequence. Many conditions are still looked on as purely medical or purely surgical in which combined surgical and medical treatment is essential to the best results.

Medicine has somewhat neglected certain phases of physical and psychical therapy and since these constitute important planks in treatment the opportunity has been seized from without, for the establishment of certain cults. The most important so-called therapeutic cults have their foundation in one or the other of the well known but unfortunately somewhat neglected therapeutic principles. For their existence we as a profession are responsible. Treatment must be comprehensive and include in its armamentarium all measures capable of affording relief.

Drugs find their most extensive application in the field of medical

treatment, but to the thinking physician treatment no longer consists merely in giving drugs or applying other measures of relief. The essence of treatment consists in recognizing the pathologic process; in understanding its causes, the mechanism involved in its production and the development of its clinical manifestations; in knowing the character, extent, and probable outcome of the resulting functional and morphologic changes; in valuing correctly the significance of clinical and laboratory findings; in ascertaining the indications for, in knowing the mode of action of, and in applying the most effective measures for its prevention, abortion, amelioration, or cure. As medicine becomes more rational it becomes more effective and drugs play a relatively smaller but better defined part. The essentials of good treatment are: correct and early diagnosis; a true conception of the cause and nature of the derangement; familiarity with the manner by which the derangement can be corrected, and the knowledge of and ability to apply the most effective measure of relief.

Factors responsible for retardation in medicine.—Since time and space preclude anything approaching an historical review, let us consider briefly on the one hand the most important factors responsible for retarding progress, and on the other the channels through which progress in treatment has come. Medicine marches with science. Since science is a matter of evolution, progress has come but slowly, and ignorance, always the chief barrier to progress, still prevails in proportions inverse to the advancement of science. While ignorance is negative in character it gives free rein to many human frailties and prejudices, to credulity and superstition which admit free dissemination of falsehood, the combination standing for inertia if not for stubborn opposition.

Belief in the supernatural origin of disease and superstition saddled the world with demons, witchcraft, spells, astral influences, magic art, and occult sciences which resulted in treatment by the use of seals, charms, talismans, incantations, and invocations. Absurdity reached its climax in the administration of drugs according to the signs of the zodiac. An inordinately credulous public and charlatanism within our ranks made possible the perpetration in the name of medicine of such hoaxes as signatures, similars, sympathetic ointments, and Perkins' tractors. That this credulity still persists is evidenced by the fact that similar cults still flourish. In the development of Christian Science there is nothing surprising except that it has developed in an age of

enlightenment rather than in the dark ages. From this we learn that scientific enlightenment has not penetrated deeply into the masses and that further instruction of the public is sorely needed in matters pertaining to medicine and sciences.

Failure to appreciate duly the self-limited character of the majority of diseases, that is to appreciate the "Vis medicatrix naturæ" of Hippocrates, has constituted a fundamental oversight and made possible the many systems within and the many cults without, which have obstructed the road of medicine. Therapeutic investigation unless adequately controlled leads usually to false doctrines.

In the final analysis it is seen that the fundamental factors responsible for the tardiness of medical progress have been: (1) the inadequacy of science, during its early period of development, to cope with the complex problems of the human organism and with the processes of life and of disease; (2) the incorrect method of approaching the subject, that is, the employment solely of speculation uncontrolled by observation and experimentation. Our forefathers erred in accepting supernatural influences as the cause of disease, in adopting a speculative philosophy instead of investigation and in the employment of measures of relief, about which they knew little, for diseases about which they knew less.

THE CHANNELS THROUGH WHICH PROGRESSIVE TREATMENT HAS COME

Progress comes through investigation, but to the public generally medical investigation makes no great appeal. The research worker is commonly regarded as impractical, yet the routine practice of today is based on the investigation of yesterday. Wassermann tests, spinal fluid studies, renal functional tests and the use of antitoxins, of glandular extracts and of arsphenamin, constitute substantial phases of medical practice today, yet we did not employ any of them a generation ago. The public and many physicians failed to recognize that progress comes through investigation, that practice is based on investigation, and that medical investigation means better care of the sick, greater public health, and happier communities.

1. *The evolution of science and the adoption in medicine of scientific methods.*—With Harvey commences experimental medicine. Demonstration and proof were subsequently demanded, theories and authorities failing longer to satisfy the profession. The "Anatomical exercise on the motion of the heart and blood in animals," 1628, ushers in a new

physiology and the science of medicine. The profession was loath to accept, but Harvey defended his thesis despite bitter opposition, and in so doing demonstrated for all time the advantages of the experimental method.

But in the seventeenth century medicine probably profited as much from without as from within. Not alone were needed experiment and demonstration but also training in methods of thought. This was supplied by Bacon* and Descartes, the former formulating "The principles of inductive science," and the latter clearly distinguishing the materialistic from the vitalistic. Galileo was creating the sciences of physics and mathematics while Sanctorius through his assistance was applying the thermometer and the scales to physiology. Borelli was utilizing mechanics and physics in investigations of the mechanics of motion. In other words, science was in the making and the instruments and methods of science were coming into general use in medicine. Alchemy was giving way to chemistry. Iatro chemistry, mathematics, and physics were laying the foundation of a new science and this in turn was permeating medicine. Medicine passed beyond the "conjectural art" of Celsus into the realm of science.

2. *Development of clinical medicine.*—Through following in the steps of Hippocrates, Sydenham became the father of clinical medicine. Observation and careful clinical records resulted in the recognition of new diseases and in the clear differentiation of known diseases. His teachings pervaded the whole realm of clinical medicine and constituted a great impetus, while the contributions of Auenbrugger, Corvissart, and Laennec placed physical diagnosis on a firm basis. Diagnosis improved as the result of better histories and clinical records, more thorough physical examinations and appropriate laboratory studies. The fundamental sciences developed and shed much light on the nature of pathologic processes. As a result disease was recognized earlier, was understood better, and was treated on more rational lines.

3. *The development of pharmacology.*—Although the use of drugs comes down from antiquity, the science of pharmacology is of recent development. Magendie, a pupil of Bichat, fired by his spirit, accomplished for treatment what Bichat had accomplished for pathology,

* Macaulay has discussed the nature of the service rendered society by Bacon. He says, "It was not by furnishing philosophers with rules for performing the inductive process well, but by furnishing them with a motive for performing it well, that he conferred so vast a benefit on society."

namely, laid the corner stone of an underlying science. In his epoch-making investigations on Upas his object was to ascertain the seat of action of the drug and in his experiments he located the seat of action of Upas (strychnin) in the spinal cord. The next step was taken by Claude Bernard, a pupil of Magendie, who in 1844 localized the action of curare in the neuromuscular endings. Schmeideburg next entered the field and studied the action of drugs on the frog's heart. He and his pupils exercised a great influence on pharmacology and have been largely responsible for its present stage of development.

Pharmacology is the science of the action of drugs. It utilizes the tools of science, observation, investigation, experimentation, standards, and measurement. It ascertains facts concerning changes in function wrought through the action of drugs, determines the seat of action and the mechanism whereby changes are effected, and not infrequently sheds light on the nature of both physiologic and pathologic processes. It has resulted in rational drug therapy and in the deletion of much empiricism and many drugs. More than any other factor it has established dosage and channels of administration.

4. *The relation of chemical constitution to pharmacologic action.*—To permit any action of drugs the living cell and the chemical molecule must come in contact. The cell may be looked upon as the participating seat of the microchemical reactions. In it are chemicals undergoing reactions which result in the development of forces, and to it are constantly added new chemicals resulting in modification of reactions and in gross modifications of physiologic functions and properties.

In 1859, Stahlschmidt demonstrated that strychnin loses its tetanizing action when a methyl group is introduced and that the new compound assumes a curare-like action. Crum, Brown, and Fraser in 1868, in view of the ammonium base formed in this reaction, investigated other similar bases derived from alkaloids, brucin, morphin, and thebain, and discovered that all quaternary ammonia bases paralyze motor nerve-endings, thus exerting a curariform action. This epoch-making discovery called attention to the relation of pharmacologic action to chemical constitution and constituted the beginning of rational synthetic pharmacology.

Ehrlich, in 1898, enumerated five important instances selected from the whole field of therapy in which a relationship was established between chemical constitution and pharmacologic action. Since that time this number has been multiplied many fold and innumerable chemical

compounds have been synthesized in the effort to obtain drugs with specific properties. Many drugs have been analyzed, that is, dissected into their component parts, and the specific action of the drug as a whole determined as a property of one of its radicals. Thus Ehrlich was able to synthesize arsphenamin and thus Macht recognized the importance of the benzyl group in opium. Such discoveries have resulted in the introduction into clinical practice of many drugs, among them arsphenamin, neo-arsphenamin, benzyl alcohol, and benzyl benzoate.

Many isolated instances of the effects of chemical constitution and of chemical configuration on pharmacologic action are known. However, in a broad sense the progress has not been great as yet. We have, as it were, but a vision of the promised land.

5. *The discovery of microorganisms and of their relation to disease.*—The discoveries of Pasteur revolutionized medical conceptions and doctrines and resulted directly in the development of bacteriology and immunology. They are responsible also for many effective public health measures, and underlie the principles of aseptic and antiseptic surgery.

Immunotherapy at present is sharply differentiated from pharmacology. It deals largely with the nature of infecting agents, with the mechanism of infection, and with specific immunity reactions. Immunity processes are undoubtedly chemical or physiochemical in character, but are as yet but little understood. As more light is shed on these subjects immunology and pharmacology will probably become more closely allied.

6. *Aseptic and antiseptic surgery.*—Following the work of Pasteur and the adoption of the germ theory, Lister applied antiseptic principles to surgery. Aseptic surgery, in reality a form of preventive medicine, proved so effectual that antisepsis did not receive the attention it actually merited. With the advent of war came the need for antiseptic surgery. For obvious reasons asepsis was unattainable and Lister's doctrines and methods were tried, but with disappointing results. Failure at first was ascribed to technical inadequacies, but later to incorrectness of principles. Indeed, one eminent authority insisted that "the treatment of suppurating wounds by means of antiseptics is illusory, and that belief in its efficacy is founded upon false reasoning." Lister's clinical observations and experiences were forgotten, and were replaced by theories and by experiments in vitro, which failed to approach the actual conditions confronting the surgeon.

However, the problems were attacked by Carrel and Dakin on simple grounds, by utilization of a substance, non-irritating to the tissues and with sufficient bactericidal power to kill all varieties of microbes present in wounds. Dakin set about finding such a substance and Carrel to elaborating the most effective manner of applying it. The problem was chemotherapeutic in nature. Methods such as were employed by Ehrlich were adopted and various antiseptics were tried. The most desirable was selected, and so modified as to meet most effectively the conditions confronting the surgeon. As a result the Carrel-Dakin method of antiseptic treatment was evolved, and the chloramins assumed a position of considerable importance in surgical practice.

7. *Specific chemotherapy.*—The surest and usually the shortest approach to the specific treatment of any disease lies through the application of experimental therapy to the experimentally induced disease in animals. Thomas of the Liverpool school of tropical medicine used atoxyl with good results in experimental trypanosomiasis, but sought other arsenical compounds less toxic for the host and more toxic for the parasite. Ehrlich, recognizing the true constitution of atoxyl, undertook its modification and in the course of some years produced several arsenicals less organotropic and more parasitotropic than atoxyl. His researches resulted in the discovery of arsphenamin and in its universal acceptance in medical practice. In his work many principles were evolved which will prove of the greatest significance to further progress in the field of specific chemotherapy.

8. *Nutrition. Metabolism.*—Where there is life there is chemical reaction, the sum total of which we term metabolism. Derangements of metabolism result often in the appearance of disease. The nature of the derangement has been ascertained in some instances. Through the development of knowledge relating to metabolic diseases and to the nature and the caloric value of food-stuffs, regulation of diet has developed along rational lines and has resulted in definite control of the course of disease in many instances. Recent investigation has revealed the fact that normal control of various phases of metabolism is exercised by internal secretions or specific substances produced by the glands of internal secretion. Perversion of these secretions leads to disease. Thus, through the employment of thyroxin, myxedema readily yields to treatment and through the use of extract of the posterior lobe of the hypophysis diabetes insipidus is readily controlled temporarily. Little is known concerning the action of drugs on metabolism, but since the

synthesis of thyroxin and epinephrin has already been effected, it would appear that the day of drug control of metabolism is close at hand.

For normal metabolism the so-called vitamins are essential. Neither their character nor the mechanism of their action is known. Their withdrawal from the diet results in the appearance of one or the other of the so-called deficiency diseases, while their reintroduction into the diet after their prolonged absence frequently results in cure. Here again it is but a question of time before definite chemical compounds will replace the substances now classed as vitamins.

Functional conception of disease.—Recognition of the functional factors in disease is rapidly obtaining a strong foothold in medicine and is replacing the structural conception which by virtue of its very nature is entirely unsympathetic to drug therapy. While a knowledge of morphologic pathology is essential to medicine, it tends more to surgical treatment or to no treatment at all. However, the recent developments of pharmacology and the ascendancy of physiologic and chemic trends in medicine (including pathology) have resulted in a more wholesome attitude toward drug treatment. In its beginning at least disease is derangement of function. Drugs cope more satisfactorily with derangements of function than with those of structure. The maintenance of function compatible with life, in spite of the existence of definite or even advanced structural changes, constitutes true therapeutic achievement.

LINES OF FUTURE DEVELOPMENT

The broadening of the scope of pharmacology.—In the use of drugs the general practitioner is the final court of appeal.* As a rule, however, drugs should never come into general use unless they are of unquestionable merit. The welfare of the public demands preliminary experimentation and adequate control. The results in ten well controlled cases are of more value than the haphazard impressions from a thousand cases. The possibilities relative to the true value of drugs can be ascertained best by those trained in the field of experimental therapy. The channels through which drugs are introduced into general use are of considerable consequence. For instance, Ehrlich not only made brilliant discoveries, but showed great insight in the selection of chan-

* As a matter of fact, highly trained clinicians exercise a profound influence on therapy, and it would be better if they constituted the last court of appeal.

nels through which arsphenamin was safely and quickly introduced into practice.

Fundamentally, disease rests on functional and structural changes secondary to physicochemical reactions. Pharmacology deals with the influence of chemical or if you please physicochemical agents on the organism. In the past pharmacologists have limited their activities, as a rule, to ascertaining the effect of these agents on healthy animals. It is now recognized that this was a great mistake. The transferring of results from mice to man and from arterial rings to the intact animal is not always justifiable or possible. For this the pharmacologists are not to blame since the opportunity for studying the action of drugs in naturally induced diseases is afforded them but rarely.

By training, pharmacologists are better equipped than any other class of medical men for ascertaining the effect of drugs on disease. But access to clinical material is usually lacking, and in consequence their training is lost to medicine so far as experimental therapy is concerned. Obviously in this connection the initiative must come from the clinic itself. The broadening of the scope of pharmacology involving inclusion of experimental therapy and access to wards would accomplish much for the advancement of medical treatment and result in such influence as that exercised by Cushny and McKenzie in England, and Hatcher and Eggleston in this country.

Guidance in the use of new drugs.—Drugs enter practice through two channels, through science and through commerce. In their entrance through scientific channels exaggerated therapeutic claims relative to their value are made at times, as the result of a lack of critical judgment and of adequate controls. But in their introduction through commercial channels financial considerations and lack of true appreciation of the fundamental problems preclude unbiased evaluations. To-day many proprietary drug interests are not content to supply the demand as in olden days, but they deliberately attempt to create a demand. As a result the general practitioner is placed in a peculiar dilemma; besieged daily by advertising matter, reeking with scientific patter, he falters between the teachings of medicine and the alluring claims of advertising agencies.

The confidence to be placed in any information depends largely on its source. Too frequently commercial advertising is utterly misleading. It would be unfair, however, to assume that all drug advertising falls into this category, for many drug houses have secured

the services of medical men of excellent training and of high ideals to assist in the preparation and marketing of their products. The good ethics of a small proportion of commercial concerns precludes wholesale denunciation, and to a certain extent makes possible success for other concerns lacking ethics.

In many instances it is difficult to determine whether new medicinal articles are or are not of merit. To assist in this undertaking the American Medical Association has created the Council on Pharmacy and Chemistry. It consists of a body of men selected because of their special knowledge of one or more fields of drug therapy. Originally their functions were somewhat analogous to those of a vigilance committee. The objects of the Council are: to protect the profession and public against fraud, undesirable secrecy, and objectionable advertising in connection with proprietary medicinal articles.

The Council stands for simplicity in drug therapy and for the use of useful drugs only. To this end it has published a small volume called "Useful drugs" in which are presented the drugs which in the opinion of the Council merit a place in this category. The preparations listed therein should receive major consideration in all courses in pharmacology and therapeutics and also in the actual treatment of the sick as carried out by practitioners. In addition, the Council brings together annually in a second volume "New and non-official remedies," such new remedies as comply with the requirements of the Council and can establish their eligibility. Admission of medicinal articles to "N. N. R." does not carry with it a recommendation on the part of the Council, but indicates only the ethical standing of the preparation.

These two small and inexpensive volumes, "Useful drugs" and "New and non-official remedies," are published by the Council. They should form a part of every physician's library, and should serve as a guide in the use of remedies, old and new. Their wide-spread adoption will do much for the wiser use of drugs.

The adoption of sound therapeutic principles in teaching and practice.—Sound teaching regarding the nature of disease and the influence of drugs will take care of many of our present difficulties. This involves leadership in the realms of therapeutics as well as in the fields of physiology and pathology. Therapeutic nihilism breeds poor treatment. The failure of clinical teachers to utilize useful remedies engenders haphazard therapy by the physicians of the future. Proper teaching

will prove the most effective weapon in combating the evils in advertising.

The physician must be brought to feel the responsibility for treatment as well as for diagnosis and to accord treatment the same time and effort afforded to diagnosis.

Strict attention to the indications of the case is of importance. The intelligent selection and administration of therapeutic agents with due appreciation of the work to be accomplished and of the results to be expected will result in greater progress. In this connection Dr. Barker's classification of drugs into first, those that destroy the cause, second, those that restore disturbed function, third, those that help to regulate the vital processes, and fourth, those that relieve symptoms, should prove of definite value. Treatment should be conducted as a matter of scientific investigation. Drugs should be used to accomplish certain results and the results should be checked.

The therapist must deal at times with intangible qualities such as strength and reserve force and at times proof of improvement is subjective only. It cannot be emphasized too strongly, however, that therapeutic success should be measured objectively whenever this is possible. In many instances new methods should be devised for this purpose. Graphic records, whenever possible, are of great value especially for purposes of comparison.

Dosage and channels of administration must receive more consideration. The $\frac{C}{T}$ of Ehrlich, the dose curative as related to the dose tolerated, must play an increasing rôle and will greatly modify dosage. Its application has already resulted in fundamental changes in the dosage of digitalis and in the relatively tremendous doses of sodium iodid now in use in the treatment of syphilis.

In the use of complex medicinal compounds standardization is essential in order to furnish units of measurement for use in dosage, and its wide-spread use is only a matter of time.

The need of a National Institute for the study of drug therapy.—The complexity of the human organism of life's processes and to a less extent, of drugs, demands a breadth and depth in investigation the details of which are beyond the grasp of one individual. Group investigation is as greatly needed as group practice. In chemotherapy, chemistry and experimental medicine are represented. Chemical detail is best handled by chemists and therapeutic detail by physicians and pharmacologists. Each deserves the best individual effort of specialists,

but the results need correlation. A National Institute of Pharmacology and Experimental Therapeutics would prove of inestimable value to American medicine.

CONCLUSION

In drug therapy recent progress has been both rapid and great. Much has been accomplished. Much remains to be done before medicine attains its goal and converts the healing art into the healing science.

THE USE OF DRUGS IN INFANCY AND CHILDHOOD *

HENRY F. HELMHOLZ

In times past many have considered pediatrics nothing more than the practice of internal medicine with a formula for the reduction of the dosage of drugs. Within the last twenty-five years, however, there has been a tremendous development in this branch of medicine. A visible manifestation of this development is the establishment of special chairs in universities, both in this country and abroad. Perhaps the most important development of the intensive work in pediatrics has been in the realm of preventive medicine; drug therapy has not kept pace with the progress in other fields of this specialty. The interest which the profession at large has taken in pediatrics is perhaps best illustrated by the establishment of local and regional pediatric societies.

The literature of the last few years on drug therapy in infants and children indicates the very slight effort that has been made in recent years in the development of such therapy. The lack of interest in this work during the rapid expansion of pediatrics in general is therefore evident.

RELATIVE DOSAGE

The main point in the administration of drugs to infants and children still is the reduction of the adult's dose. Drug therapy in infants and children, therefore, not only shares all the faults it has in the adult, but since the various formulas for calculating the dosage are based on weight or on age, or on weight and age, a specific error is introduced, for the child is not a pocket edition of the adult and the two cannot be compared pound by pound. During growth the relationship of the various organ-systems of the body to one another shifts, and with this process the relationship of each organ-system to the whole

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body shifts. For instance, in the newborn infant about 23 per cent of the total weight is in the muscles, in the adult about 43 per cent is in the muscles. The relative weight of the infant's liver is about two and one-half times greater than that of the adult. This is of great importance, for a number of drugs do not distribute themselves equally over the body, but have certain affinities for various tissues or constituents of tissue. The affinity of many narcotics for lipid tissue is well known. Some further factors enter into consideration. The administration of chloroform to an adult dog readily produces necrosis of the liver, but the production of this necrosis of the liver is far more difficult in the pup, where the relative large amount of glycogen exercises a protective influence.

It is stated that certain drugs are well tolerated by the infant, while others are not. This statement also rests on a comparison with dosages for adults, and emphasizes the necessity of a study of the pharmacologic action of various drugs in the infant. The functional activity of some organs develops in the course of growth like that of the sexual glands. Their internal secretions exercise an influence on the organism, and, while it is a fact that we know the chemistry of the secretions of only two glands, the suprarenal and the thyroid glands, we must assume that the activity of the secretions of other glands also depends on one or more chemically well defined substances. These substances, whatever their derivation, may have a decisive influence on the reaction of the organism to drugs. In this connection the results of Le Heux, from the laboratory of Magnus, are of the greatest importance. They confirm the theory that sodium salts of acetic acid and pyruvic acid increase the stimulation of the isolated intestine and supply strong evidence to indicate that this stimulation is due to the formation of ester of acetic acid and pyruvic acid with the cholin normally present in the intestinal walls. These factors are sufficient to prove that the administration of drugs to infants by formula is very unsatisfactory and depends entirely on chance. Drug therapy in the infant has suffered, like that of the adult, from a number of mistakes and fallacies. First, only a small number of drugs exercise a rapid and striking effect either by destroying the main causative agent of a disease or by producing a lasting favorable effect on it; second, there is therapeutic nihilism, which is both fashionable and convenient; some of its roots strike deep into the quagmire of muddled observations. It is a remarkable phenomenon in the history of medicine that even the keenest observers lose their power

of criticism and judgment when discussing therapy. Third, carefully controlled studies of the action of drugs in the infant and in the child exist, if at all, only in limited numbers.

DRUG GROUPS

In order to establish a standardized list of drugs essential to the treatment of the diseases of infancy and childhood I selected from the pharmacopeia a list of sixty-one drugs. This list I sent to eighty-four men who are limiting their practice to pediatrics, with the request that they check the drugs listed and add to them any drugs which they considered essential in their practice. Of the eighty-four men, sixty-four responded. I wish to thank these gentlemen for giving me the benefit of their experience. A short analysis of the responses is of interest.

Many of the drugs were grouped under special headings, such as antispasmodics, laxatives, cardiac stimulants, and antipyretics. Only mercury in some form and santonin, on the list submitted, are used by all sixty-four men. Besides these, silver, arsenic, iron, sodium bicarbonate, cod-liver oil, and at least one representative of the opium series, the antispasmodics, heart and circulatory stimulants, hypnotics, laxatives, antipyretics, anthelminitics, and urinary antiseptics, were used by sixty men of the sixty-four. One-half of the men used forty-three of the drugs indicated on the list.

A number of men added drugs to the list. Fourteen added milk of magnesia, and each of three men or more added benzyl benzoate, hyoscyamin, chloroform, agar-agar, creosote, chenopodium, glycerin, and tincture benzoin compound. One man added thirty-eight drugs to the list.

The drugs in this list can be readily divided into four groups. The drugs in the first group have specific indications; for example, mercury, arsenic, quinin, santonin, male fern, and so forth, act directly in destroying parasites, and the drugs such as silver, hexamethylenamin, and salicylates have definite antiseptic powers for destroying bacteria. The indication for the use of these drugs is usually given with the diagnosis of the disease. The drugs in the second group regulate the function of the different organs, for example, digitalis, the group of laxatives, and the diuretics. The third group is essentially for the symptomatic treatment of diseases. The fourth group consists of drugs that are used for a specific purpose and for practically no other, such as phosphorus

in the treatment of rickets and spasmophilia, mustard for counter-irritation, and phenol for the infections of the middle ear. This classification does not differ greatly from the old pharmacopeial classification of drugs which rested on the *indicatio vitalis, causalis, morbi, and symptomatica*.

It is not my object here to attempt an enumeration of the indications for the use of these various drugs. I merely wished to collect a group of drugs that, in the experience of a large number of pediatricians, covers the needs in the practice of pediatrics.

INDICATIONS FOR DRUG THERAPY

The importance of a definite indication for the use of drugs is even more essential in infants and children than it is in adults. As Dr. Jacobi has said, "Most conditions in childhood right themselves without any medication," and, "I believe we are justified in assuming that the man in general practice uses more medicine, rather than too little, for the welfare of his little patients."

The tendency toward homeopathy, particularly in the treatment of the diseases of children, so much in vogue about thirty-five years ago, when adults were treated by regular physicians and children by homeopathic physicians, was the logical outgrowth of too much medication. To-day the homeopathist, the indications for drug therapy being very much more finely drawn, has almost disappeared from our midst. The public, too, has become educated, so that, as a rule, it appreciates the advice given by the physician more than the prescription he writes.

In infancy, in particular, the use of drugs should be limited to definite indications, and these indications are usually for a single drug. The younger the child, the greater the danger of upsetting its gastro-intestinal functions by medication. Diseases of the infant, of whatever nature, frequently manifest themselves by gastro-intestinal symptoms. Indeed, in many cases they are the only symptoms, and it is very important not to derange the gastro-intestinal tract still more. The treatment of parenteral infections by repeated catharsis is perhaps the best example of the danger of treatment without a diagnosis.

PROBLEMS IN ADMINISTRATION AND DOSAGE

It has been the general experience that the difficulties of administering medicine are not so much those of giving certain medicines to

children, as those of giving any medicines to certain children. In this connection two very important points must be emphasized: first, it is usually children who are unwilling to coöperate who are unwilling to take medicine, another example of the spoiled child; and second, the physician fails to appreciate the importance of his personal relationship with his little patient. The fact that a child promises to take the medicine is very much better than any assurance on the part of the mother or nurse to administer it.

We are not limited, in our administration of medicine, to the oral route, but, as it is by far the simplest method, it is most frequently used. When a child, either because of mood or as the result of illness, is unwilling to take medicine by mouth, it can very easily be given with a nasal tube. The rectum, too, can be used as a means of administering drugs, particularly the drugs such as chloral hydrate, that are likely to irritate the stomach.

The dose of chloral hydrate by rectum as usually given is about twice the dose by mouth. Intravenous injection insures quicker action with a smaller dosage. It must be remembered, however, that for a drug to develop its pharmacologic action it must be in contact in sufficient concentration with the tissues to be acted on for a definite length of time. This means, the more rapid the absorption, the lower the dose, but, on the other hand, the shorter the action, the greater is the necessity for repetition of the dose for constant action. Another factor to be considered in this connection to the rapidity of elimination, as shown by Ramsey and Groebner's work with mercury.

The treatment by drugs of diseases in infancy is influenced in its effectiveness by the factor of nutrition and growth. This is perhaps best expressed by the statement that as long as a child eats and digests well there is a good chance for recovery. A drug which acts favorably on the disease focus, but interferes with the nutrition of the child is harmful. The effect of the so-called tonic treatment during the active stage of disease is another example of the failure to recognize the nutritional factor in disease.

I shall call attention also to the necessity of objective standards for the value of drug therapy. At present almost all our judgment is subjective, and the results of drug therapy depend to a large degree on whether the physician is an optimist or a pessimist. Until we have objective standards, the relative values of various modes of treatment must, of necessity, be difficult to determine. It behooves us all, there-

fore, to apply objective measurements, wherever possible, in our studies of drug therapy.

My original plan was to include in this paper a table of the doses of drugs for the different age periods. On second thought, however, it seemed too important a matter to be decided arbitrarily by the opinion of any one physician; such a table, dependent as it is on experience rather than experiment, is a problem that calls for coöperative effort. I was strengthened in this belief by looking over Lavaille's tables on the dosage of drugs for the first two years, which appeared in Variot's recent text book. He designates a dose for the first month; for older infants he multiplies the dose by the number of months the child is of age, merely another mode of dosage according to age without any consideration of the peculiarities of infancy and childhood.

In concluding I wish to propose that the Section on Pharmacology and Therapeutics recommend to the proper authorities the appointment of a committee for the purpose of studying the problem of the therapeutic action of drugs and their dosage in infancy and childhood.

LIST OF DRUGS SUBMITTED TO PEDIATRICIANS

	Recommendations
1. Silver.....	63
Nitrate.....	48
Argyrol.....	58
2. Mercury.....	64
Blue ointment.....	52
Calomel.....	50
Ammoniated mercury.....	55
Mercuric chlorid.....	39
3. Arsenic.....	61
Fowler's solution.....	49
Sodium cacodylate.....	24
Arsphenamin.....	50
4. Iron.....	60
Syrup of ferric iodid.....	51
Blaud's pills.....	35
Ferric citrate.....	40
5. Phosphorus.....	42
6. Cod-liver oil.....	63
7. Iodin.....	50
Potassium iodid.....	43
8. Turpentine.....	17
9. Mustard.....	49

ANTISPASMODICS

Recommendations

10. Epinephrin.....	53
11. Atropin.....	58
Belladonna.....	43
12. Magnesium sulphate.....	36
13. Calcium chlorid.....	49

STIMULANTS (HEART AND CIRCULATORY SYSTEM)

14. Camphor.....	52
15. Digitalis.....	62
16. Strophanthus.....	25
17. Nitrites.....	20

RESPIRATION (CENTRAL)

18. Strychnin (tincture of nux vomica).....	40
19. Caffein.....	50

HYPNOTICS

20. Alcohol.....	28
21. Chloral hydrate.....	55
22. Barbital.....	17
23. Luminal.....	36
24. Bromids.....	61

LOCAL ANESTHETICS

25. Procaïn.....	47
26. Ethyl chlorid.....	30
27. Orthoform.....	13

LAXATIVES

28. Castor oil.....	55
29. Senna.....	26
30. Rhubarb.....	32
31. Jalap.....	12
32. Aloin.....	3
33. Cascara sagrada.....	55
34. White liquid petrolatum.....	45
35. Sodium sulphate.....	45

ASTRINGENTS

36. Tannates.....	25
37. Bismuth.....	51
Opium series.....	62
38. Opium.....	30
Morphin sulphate.....	46
Paregoric.....	47
39. Codein sulphate.....	54
40. Heroin.....	20

RESPIRATORY TRACT

Recommendations.

41. Ipecac.....	48
42. Ammonium carbonate.....	33
43. Squills.....	14

ANTIPIRETICS

44. Quinin.....	48
45. Antipyrin.....	49
46. Phenacetin.....	36
47. Pyramidon.....	13
48. Acetylsalicylic acid.....	52
49. Sodium salicylate.....	49

ANTHELMINTICS

50. Male fern.....	62
51. Santonin.....	64

DIURETICS

52. Citrates.....	53
53. Acetates.....	34
54. Theobromin sodium salicylate.....	25

ALKALIS

55. Sodium bicarbonate.....	62
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URINARY ANTISEPTICS

56. Hexamethylenamin.....	59
57. Salol.....	30

MISCELLANEOUS

58. Menthol.....	36
59. Phenol.....	45
60. Sulphur.....	44
61. Boric acid.....	56

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THE EXAMINATION OF TEETH IN GROUP MEDICINE*

BOYD S. GARDNER

The literature on dental subjects for the last few years does not give credit to the value of full mouth roentgenograms and the necessity of such examination apparently is not entirely appreciated either by the medical or the dental professions. Certain members of both professions still consider it quite ridiculous to examine, roentgenographically, the mouth of a patient wearing a full upper or lower denture. However, Eusterman's findings, in a study of roentgenograms of the mouths of 290 patients wearing either full or partial dentures, have demonstrated the importance of this phase of our work. Obviously a full mouth examination not only is necessary, but the patient's due, if he is suffering from a systemic condition and a focus of infection is suspected. Besides this group of patients, are those who are undergoing thorough examinations from the standpoint of prevention of disease.

In diagnosing affections of the teeth the existing pathologic condition should be visualized as it is when the teeth are removed surgically. The open view operation has made this possible, since the exact condition may be seen, while with the older methods it is necessary to work more or less in the dark. For this reason it is important that the dental diagnostician should have surgical training.

If complete extraction is necessary and a full denture required, especially in elderly persons, it is well to explain carefully the probable results. Many patients are shocked by the change and regret having had the extraction. While the elimination of dental infection is of primary consideration, nevertheless, the dental surgeon should keep in mind that the patients are to have dentures and that coöperation with the prosthodontist should begin before operation. In many instances preoperative models and facial measurements are advantageous.

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It has been proved beyond doubt that a casual glance into the mouth with the idea of noting suspicious teeth, such as those supporting bridges and crowns, or holding large fillings, and so forth, is worthless. The deciding question is whether or not the clinician actually wishes to know if the teeth with their investing tissues are to be considered possible factors in the condition of the patient. This conclusion can only be reached after the examination of thousands of patients by full mouth roentgenograms. Residual roots, granulomas, and impacted teeth are often found under plates that have been worn for many years, and their removal has relieved many patients suffering from systemic disorders, particularly iritis, and one type of arthritis, neuritis, and so forth.

The roentgen-ray evidence should be carefully considered while the patient is under observation. The many advantages in checking up the clinical and roentgen-ray evidence at the same time cannot be overestimated. The full mouth roentgenogram makes it possible to compare densities, which is just as necessary in dental work as in orthopedic work, when, for example, an abnormal condition of the right knee can best be demonstrated roentgenographically by a comparison with a normal left knee. Likewise in dentistry, the lower first molar may appear to be abnormal, but on comparison with the opposite first molar one may be surprised to see that the condition is normal.

During the past year approximately 28,000 patients were examined in the Dental Section of the Mayo Clinic. A review of the histories of these patients discloses ample evidence that the usual method of extraction is far from adequate. Residual roots and granulomas as well as impacted and unerupted teeth were not infrequently found in supposed endentulous areas, as shown by Eusterman. Thirty per cent of these patients had roots, 4 per cent had impacted or unerupted teeth, and 3.5 per cent had residual granulomas. With the open view operation of extraction, which is now known as alveolotomy, it is practically impossible to overlook such conditions; this is proved by postoperative roentgenograms made routinely. The literature abounds in criticism of this method, yet when it is carried out with proper restrictions, the results are most satisfactory.

Physicians should encourage the routine examination of teeth except in hopeless or emergency cases. Time is an important factor in emergency cases; however, the dental examination can be postponed until during convalescence after operation. The condition for which the

patient is operated need not necessarily be due to mouth infection to warrant the dental examination, but the elimination of such infection is of material aid in the after-care of the patient and in the prognosis.

Oral infection cannot be eliminated by extraction alone. Treatment for pyorrhea and thorough prophylaxis are both often necessary. Great care should be exercised with regard to the number of teeth extracted at one time, and the length of time between operations. This is also true of prophylactic treatments. There should be a limited amount of scaling at the first appointment and it should not be repeated for several days.

The profession of dentistry should be discouraged from making promises to patients as to the possible result following the extraction of teeth with evidence of infection. They need the coöperation of the physician and are only responsible for the field in which they work. An intelligent report with regard to the dental findings is desired from the dentist by the physician who should take the responsibility of advising and encouraging the patient as to the outcome of the dental treatment.

The dentist in making his report divides the teeth into two groups: those which should be removed for local reasons, and those which should be removed when systemic conditions warrant the procedure. Therefore, the removal of teeth in patients in the first group is a question for the dentist to decide, providing the patient's physical condition is such that he can stand the operation, and of those of the second, for the physician. Teeth with marked evidence of infection at the roots, certain types of impactions, and teeth affected by pyorrhea to such an extent that treatment is of no avail compose the first group. In the second group are listed pulpless teeth that are negative to the roentgen ray, and their extraction is advised only when the systemic condition is traced to a focus. Thus many patients are allowed to retain pulpless teeth, which, however, should always be considered questionable. Therefore, to say that all pulpless teeth should be extracted is doubtless too radical at the present time.

CONCLUSIONS

1. It is necessary that the dental report shall be based on the roentgen ray, making use of full mouth pictures, and on clinical evidence.
2. Coöperation between the medical and dental professions is neces-

sary in order that conclusions may be reached with regard to the teeth which should be sacrificed.

3. The dentist should be discouraged from making promises with regard to the outcome of extractions.

4. The extraction of teeth by simply "pulling" is not adequate or justifiable.

5. The results from the extractions of teeth by the method known as alveolotomy should be encouraged with proper restrictions.

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FOCAL INFECTION AND ELECTIVE LOCALIZATION IN THE ETIOLOGY OF MYOSITIS*

EDWARD C. ROSENOW AND WINIFRED ASHBY

Although acute muscular rheumatism is generally conceded to be an infectious process, the myalgias and milder forms of myositis are not so definitely accepted as such. Myalgic pains are considered by Taylor to be the result of faulty metabolism, by Gordon, of excessive katabolism from overexertion of muscle cells, and by Profanter as the peripheral expression of pain due to defective function or injury of visceral organs. Except among English writers, such as Poynton, Llewellyn and Jones, Munroe and Almond, and Stockman and Renton, little credence is given to the idea of localized invasion of the muscles by bacteria other than in marked acute generalized myositis, and the condition described as dermatomyositis.

The demonstration by one of us (Rosenow)²¹ eight years ago that streptococci from patients with rheumatic fever with muscular involvement, and streptococci from patients with acute nonrheumatic myositis,¹⁹ tended to localize and produce nonsuppurative lesions in muscles of animals following intravenous injection supports strongly the infectious theory of myositis. The localization in muscles occurred with strains isolated from the focus of infection as well as those from the involved muscles.

There are many reasons for believing that chronic localized infections, such as in tonsils and teeth, play an important part in the production of pronounced and mild forms of myositis. Infections in these areas are commonly present in patients suffering from myositis. Localized myositis occurs often during certain epidemics of tonsillitis and other infections of the upper respiratory tract. Rheumatic fever in which involvement of muscles is common is usually ushered in by an attack of tonsillitis. Beneficial effects from tonsillectomy were noted by Lillie and Lyons in a study of 200 cases of myositis and arthritis, by Nordlund in thirty cases, and by Kelly in ten cases. The nature of

* This article with detailed descriptions of the important cases appears in the *Archives of Internal Medicine*, 1921, xxviii, 274-311.

the causal relationship, however, is generally considered to be other than the localization of bacteria in the muscles. Krebs and Schmidt put forward the idea that the symptoms in these conditions are due to injury of the nerves by toxins produced by the bacteria in a focus of infection.

The difficulties in studying the etiology of myositis, especially the milder forms, are many. Attacks of myositis are rarely fatal. Cultures from the blood prove negative. The lesions often occur in inaccessible parts. Removal of pieces of muscle for cultural and other studies is painful and objected to by many patients, and the isolation of bacteria free from contamination is difficult. We endeavored to obtain light on the nature of this puzzling problem by testing the effect in suitable animals of the intravenous injection of the bacteria from foci of infection, and excised pieces of muscles in cases of myositis and closely related conditions, and by noting clinically the effect on the course of the disease of the removal of the suspected foci of infection.

TECHNIC

The technic has been similar to that employed in other elective localization studies.^{18, 20} Whenever possible material obtained from the depths of the suspected focus of infection, that is, material expressed from tonsils or aspirated from the depths of pus pockets of teeth showing pyorrhea, and the washings from ground-up tonsil tissue, was injected intravenously immediately. Cultures were made in tall columns (10 to 12 cm.) of ascites-glucose broth or glucose-brain broth (0.2 per cent), and on blood-agar plates. To each tube of broth adjusted to hydrogen ion of 6.7 was added approximately 2 c.c. of calves' brain before autoclaving. The animals were injected intravenously with either the young primary broth culture or with the centrifuged organisms suspended in salt solution. From 2 to 5 c.c. of the broth culture itself, or the growth from 10 to 30 c.c. in salt solution were used routinely in average sized rabbits. The dose for guinea pigs and dogs was in proportion. Smears and blood-agar plates were made of the material injected to determine the character of the organisms and their viability. Cultures made from plated material were not used routinely, for it has been shown that the bacteria having elective localizing power may be sensitive to oxygen, especially in the primary culture, and often fail to grow on blood-agar plates, and when not aerobic cultivation has been found to destroy the peculiar patho-

genicity which enables them to invade specific tissues. In shake cultures of excised pieces of muscle in tall columns of agar the organisms may retain their viability and specific localizing power for a long time (Case 130).

Usually only one injection was given; in some instances two were given, and rarely three. The animals were often caged separately, observed for evidence of muscle symptoms, and handled with care to avoid injury. Those that died were examined as soon after death as possible. Those that survived were etherized, as a rule, in from forty-eight to seventy-two hours after the last injection, and examined at once. In special instances they were allowed to live for from ten to fourteen days. Painstaking search for local lesions in muscles and viscera was made in a strong light and the incidence of lesions recorded.

The identity of the organism causing the lesions was determined by making routine cultures on blood-agar and in tall columns of the broth of emulsion of the lesions in the muscles, of the blood (0.2 c.c.), and, in some instances, of emulsions of normal muscle, and viscera showing no lesions, and by microscopic examination of stained sections of the tissues. The organism isolated from the lesions in the muscles was frequently reinjected one or more times.

RESULTS

In this way we studied altogether twenty-eight cases of myositis, extending over a period of six years. The important clinical and experimental findings in these cases are summarized in Tables 1, 2, and 3. The age of the patients ranged from six years to sixty-five years. All but one were twenty or more years of age. Sixteen were males and twelve were females. The condition found in the patients varied from mild acute transient, often recurring, attacks of localized myositis in persons who were well otherwise, to marked chronic generalized myositis which had incapacitated them for work for several years. Some of the patients had had attacks of other diseases, such as cholecystitis, but these conditions were not present at the time their cases were studied. In six cases one or more other members of the family were similarly afflicted. There was a history of tonsillitis or sore throat in relation to attacks or exacerbation in ten cases. The tonsils were usually small and appeared quite normal on inspection, but by means of pressure pus was often expressed, especially from the pole, indicating probable absorption of bacteria and their products.

The tonsils alone were removed as the focus of infection suspected of having causal relationship in thirteen cases, teeth alone in four cases, and infected teeth and tonsils in eight cases. In three cases no foci were removed. In these cases the muscle trouble was preceded by tonsillitis in two, and nasopharyngitis in one.

The extirpated tonsils often showed one or more abscesses near the base. The infections of the teeth included pyorrhea (Case 601), infection of the pulp without apical rarefaction (Case 567), and apical infections of artificially devitalized teeth (ten cases). Of the twenty-five patients from whom one or more suspected foci were removed improvement or complete recovery, which was attributable to this treatment, occurred in twenty-two. In two (Cases 602 and 898) the result is unknown, while in one case (Case 572) no improvement followed. The improvement in many instances occurred promptly, especially in the more acute cases. In the more chronic and more extensive infections the improvement was slow and sometimes did not become apparent until several months had elapsed. The good effects were not merely temporary; complete recovery has lasted in many of the cases for a number of years. In three cases partial recovery noted after a previous tonsillectomy became complete, or additional improvement occurred following the removal of the dental infections (Cases 567, 623, and 4132). In two patients complete restoration to health followed removal of tonsillar tissue which remained after defective tonsillectomy, and the removal of one or more infected teeth (Cases 369 and 622).

In all cases but one, a patient with spasmodic torticollis (Case 572), in whom no improvement followed tonsillectomy, elective localization of bacteria from foci or from excised muscle occurred following their intravenous injection into animals. Of the twenty-seven positive cases the streptococcus was found to have elective affinity for the muscles in twenty-four cases, streptococcus and staphylococcus in two, and staphylococcus alone in one.

The streptococcus produced two types of colonies on blood-agar plates, one, a small colony surrounded by a narrow and usually a somewhat hazy zone of hemolysis, the other, a slightly larger, but dry colony surrounded by a greenish zone. The muscle lesions in animals were caused by the slightly hemolyzing streptococcus in ten cases and by the green-producing type in ten cases; in four both varieties were present; in two cases the hemolyzing streptococcus and staphylococcus (Case

TABLE 2
SUMMARY OF CLINICAL AND EXPERIMENTAL FINDINGS IN CASES OF MYOSITIS AND ARTHRITIS

Case.	Sex and age.	Clinical findings.	Foci removed.	Result.	Bacteria having elective localizing power.	Animal experiments.													
						Animals injected.	Number showing lesions in												
							Joint fluid (turbid).	Periarticular ligaments.	Muscles.	Nerves.	Stomach and duodenum.	Kidneys.	Lungs.	Thyroid.	Skin.	Pericardium.	Myocardium.	Endocardium.	Other organs.
A164	M. 40	Recurring localized myositis; subacromial bursitis; typical painful abscesses in tonsils; infected devitalized teeth; painful bleeding hemorrhoids, with superficial ulceration.	Tonsils and two infected teeth.	Marked improvement.	Slightly hemolyzing streptococcus from tonsils and teeth.	8	2	1	5	0	3	0	0	2	0	0	1	2	Gallbladder in one.
A369	M. 25	Chronic localized myositis, chiefly of muscle insertions around joints, and chronic arthritis.	Tonsils, tonsil tag, and infected tooth.	Improvement after tonsillectomy; complete recovery after removal of tonsillar tag and tooth.	Green-producing streptococcus from tonsils, tooth, and joint fluid.	8	4	2	4	0	3	1	0	0	2	3	3	2	
A336	M. 27	Muscular and articular rheumatism for three years; repeated attacks of tonsillitis.	Tonsils.	Decided improvement, but not complete recovery.	<i>Streptococcus aureus</i> from tonsils.	4	2	1	4	0	1	2	0	0	0	0	3	1	Bladder in one.
A542	F. 42	Repeated attacks of rheumatic fever, preceded by attacks of sore throat; chronic myositis and arthritis, chiefly of knees, elbows, shoulders, and back; hypertrophic rhinitis; follicular pharyngitis; large septic tonsils; two abscessed teeth.	Tonsils and two abscessed teeth.	Gradual improvement after tonsillectomy; rapid improvement after removal of abscessed teeth.	Slightly hemolyzing streptococcus from tonsils and teeth.	1	0	1	1	0	0	0	0	0	0	0	0	0	
A543	M. 65	Chronic myositis and periarthritis; septic tonsilla	Tonsils.	Marked improvement.	Slightly hemolyzing streptococcus from tonsils.	2	1	1	2	0	0	0	0	0	0	0	1	2	Gallbladder in one.

SUMMARY OF CLINICAL AND EXPERIMENTAL FINDINGS IN CASES OF MYOSITIS AND ARTHRITIS—Continued

A552	M. 51	Rheumatic fever when a child; repeated attacks of muscular and neuralgic pains; lumbago and sciatica for twelve years; repeated sore throat; pericarditis three years before; myositis and arthritis of right knee, but no sciatica at time of examination; abscesses in tonsils.	Tonsils.	Complete recovery soon after removal of tonsils five years before.	Green-producing streptococcus from tonsils.	2	1	0	2	0	1	0	0	0	0	1		
A621	F. 53	Chronic localized myositis; periarthritis, and arthritis; tonsillectomy seven years before, with temporary improvement; infected tonsil tissue at base of tonsillectomy scar; dental abscesses.	Tonsil tag and two infected teeth.	Decided improvement, but not complete recovery.	Green-producing streptococcus from tonsils and infected teeth.	4	3	3	2	0	1	0	0	0	0	1	Appendix, and hyperemia of pulps of teeth, one each.	
A622	M. 42	Chronic recurring localized myositis; subacromial bursitis, and low-grade peripheral arthritis of fingers; tonsillitis; infected tonsillar tissue following incomplete tonsillectomy; dental infection.	Tonsils, and infected, devitalized teeth.	Repeated improvement of systemic condition following removal of foci.	Slightly hemolyzing and green-producing streptococcus from tonsils and teeth.	17	3	5	12	0	0	1	2	0	0	1	Burse in nine; bladder in one.	
A898	F. 34	Chronic arthritis and myositis; marked exacerbation following quincy three months before; tonsils small and ragged; apical infection of two devitalized teeth.	Tonsils.	Unknown.	Green-producing streptococcus from tonsils.	1	0	0	1	0	0	0	0	0	0	1	0	
A913	F. 37	Chronic localized myositis; periarthritis, and bursitis; submerged, small, septic tonsils.	Tonsils.	Complete recovery.	Slightly hemolyzing streptococcus from tonsils.	12	1	5	11	0	1	1	1	0	1	1	Burse in four; lymph glands in two; spleen in one.	
A922	F. 64	Chronic myositis and arthritis and paralysis sciaticus.	One infected tooth.	Temporary improvement of joint and muscle symptoms.	Green-producing streptococcus from tooth.	2	0	0	2	0	0	0	0	0	0	0	0	
				Total	(11 cases)	61	17	19	46	0	10	5	3	2	3	4	12	8

TABLE 3
SUMMARY OF CLINICAL AND EXPERIMENTAL FINDINGS IN CASES OF MYOSITIS AND NEURITIS

Animal experiments.																			
Case.	Sex and age.	Clinical findings.	Foci removed.	Result.	Bacteria having elective localizing power.	Animals injected.	Number showing lesions in												
							Joint fluid (turbid).	Periarticular ligaments.	Muscles.	Nerves.	Stomach and duodenum.	Kidneys.	Lungs.	Thyroid.	Skin.	Pericardium.	Myocardium.	Endocardium.	Other organs.
A567	F. 28	Neurasthenia; migraine; recurring acute myositis of muscles of neck, asopod muscles of neck, associated with dental neuritis or facial neuralgia; cervical lymphadenitis; colloid goiter; three infected dental pulps; previous tonsillectomy with improvement.	Infected teeth.	Marked improvement, but not complete recovery.	Slightly hemolyzing streptococcus from teeth, and excised muscle.	23	0	1	15	12	3	3	1	0	0	0	0	0	Teeth in elevator in two; adrenals; spleen, and lymph glands, one each.
A571	F. 22	Neurasthenia; migraine; pains in muscles of chest, especially the left side, and in the back; numbness of right arm, especially when fatigued and nervous; hacking cough, and nausea; infected tonsils; cloudy right nostrum.	Tonsils.	Marked improvement.	Green-producing streptococcus from tonsils.	5	2	1	5	2	1	1	1	0	0	0	1	1	
A572	M. 43	Spasmodic torticollis for four months.	Tonsils.	No change in condition.	None.	2	0	0	0	0	0	0	0	0	1	0	0	0	
A601	M. 43	Repeated attacks of muscular rheumatism for years; at time of examination impaired conduction and heart block; marked pyorrhea; apical infection of three teeth.	Three teeth; prophylactic treatment of pyorrhea.	Marked improvement lasting two years.	Slightly hemolyzing streptococcus from teeth.	13	0	0	7	2	3	0	5	0	0	3	5	0	Spinal cord, aorta, intestines, two each; gall-bladder, thyroid; mesenteric lymphatic fat, one each.

SUMMARY OF CLINICAL AND EXPERIMENTAL FINDINGS IN CASES OF MYOSITIS AND NEURITIS—Continued

A923	M. 44	Neurasthenia; lack of endurance; muscular pains, especially of the chest and shoulders; numbness in arms at times; apical infection around three teeth; septic tonsils.	Tonsils, and three infected teeth.	Gradual improvement.	Green-producing streptococcus from tonsils and teeth.	4	2	0	3	0	1	0	0	0	0	0	0
A2291	M. 49	Neurasthenia; lack of endurance; muscular and nerve pains in lumbar region and thighs; septic tonsils.	Tonsils.	Gradual improvement.	Staphylococcus aureus from tonsils.	2	0	0	2	1	0	0	1	0	0	0	0
A1132	M. 52	Acute localized myositis and dental neuritis; previous tonsillectomy, with improvement.	Three infected teeth.	Prompt improvement.	Green-producing streptococcus from teeth.	2	0	0	2	1	0	0	0	0	0	0	Teeth in two.
			Total		(7 cases).....	51	4	8	34	18	8	4	8	0	1	3	6 7

602) were responsible; in one the *Staphylococcus aureus* alone (Case 536) was the causative factor.

In most instances the details of the patients' symptoms were not known to us when the results of the experiments were recorded. In reviewing the clinical histories we found that the cases fell into three quite distinct groups. The cases in Group 1, summarized in Table 1, comprise the cases of acute and chronic myositis without other demonstrable lesions at the time of study. In Group 2 (Table 2) are the cases that presented predominating symptoms of myositis, but in which periarthritides and arthritis were also present. In Group 3 (Table 3) are the cases in which the findings were chiefly those of myositis, but in which symptoms of mild neuritis or perineuritis were also present. The incidence of lesions in each of the three groups is given in Tables 1, 2, and 3. It will be noted that in Group 1, the pure myositis group, seventy-nine (88 per cent) of ninety animals injected had lesions in muscles, fourteen (16 per cent) had turbid joint fluid, and only 1 per cent had lesions in nerves. In Group 2, that of myositis and arthritis, lesions of muscles occurred in forty-eight (79 per cent) of the sixty-one animals injected, seventeen (28 per cent) had turbid joint fluid, and none developed lesions in nerves. In Group 3, that of myositis and neuritis, lesions in muscles developed in thirty-four (67 per cent) of fifty-one animals, only four (8 per cent) had turbid joint fluid, and eighteen (35 per cent) had lesions in nerves or nerve sheaths. The incidence of lesions in the periarticular ligaments in the three groups was 6, 31, and 16 per cent respectively. This parallels quite closely the patients' symptoms not only with regard to the chief lesions in the muscles but also in the minor lesions, such as those joints in the arthritis group and nerves in the neuritis group.

In Table 4 is summarized the total incidence of lesions in the three groups of cases of myositis, and, for purposes of comparison, the incidence of localization in similar experiments in ulcer of the stomach, cholecystitis, appendicitis, poliomyelitis, and of streptococci from similar sources from persons having miscellaneous diseases, and from normal persons. Among the diseases studied in the miscellaneous group were acute myelogenous leukemia, urticaria, ulcerative colitis, bronchitis, elephantiasis, thyroiditis, diabetes, purpura, jaundice, epididymitis, acute pyorrhea, dermatitis, and angina pectoris. The incidence is given in percentages, so the figures are directly comparable. Thus, of 202 animals injected with twenty-eight myositis strains, 161

(80 per cent) developed lesions in muscles, and sixty-seven (33 per cent) developed arthritis, manifested by turbidity of joint fluid, or by hemorrhages in the periarticular ligaments. The total incidence of lesions in the muscles in each of the other diseases studied, and in the miscellaneous group, is much lower, varying from 4 per cent in ulcer to 16 per cent in acute poliomyelitis. The high figure in each of the other diseases corresponds to the disease the patients were suffering from at the time of the experiments. Thus in ulcer 68 per cent of the 168 animals developed lesions in the stomach or duodenum; in cholecystitis 80 per cent of forty-one animals developed cholecystitis; in appendicitis 70 per cent of seventy-one rabbits developed lesions in the appendix; in acute poliomyelitis 46 per cent of 123 animals developed lesions in the central nervous system. This is in sharp contrast to the results obtained following the injection of 212 animals with seventy-one strains from miscellaneous sources. In these, as shown in the last line in Table 4, no particular organ was attacked. The incidence of lesions of 12 per cent in voluntary muscles is about that shown in Henrici's tables following injections of plated streptococci from miscellaneous sources. The myocardium in the myositis group had lesions, often marked, in thirty-four (17 per cent) of the animals, which, as might be expected, is a considerably higher incidence than occurred following the

TABLE 4

ELECTIVE LOCALIZING POWER OF STREPTOCOCCI FROM MYOSITIS AS COMPARED WITH STREPTOCOCCI FROM OTHER SOURCES

Source of streptococci.	Strains.	Animals.	Percentage of animals showing lesions in.												
			Muscles.	Joints and ligaments.	Nerves.	Stomach and duodenum.	Gallbladder.	Appendix.	Kidneys.	Lungs.	Skin.	Pericardium.	Myocardium.	Endocardium.	Central nervous system.
Myositis	28	202	80	33	9	13	3	1	9	7	4	4	17	8	?
Ulcer of the stomach	37	168	4	12	0	68	21	1	3	0	0	2	3	10	?
Cholecystitis	12	41	7	17	0	29	80	0	5	5	2	0	2	10	?
Appendicitis	17	71	12	29	0	11	1	70	0	0	0	0	9	21	?
Acute poliomyelitis	22	123	16	15	4	13	2	2	2	11	0	5	7	7	46
Miscellaneous	71	212	12	9	4	9	1	1	9	7	4	0	4	12	?

injection of other strains; in the case of ulcer it was 3 per cent, in cholecystitis 2 per cent, in appendicitis 9 per cent, in poliomyelitis 7 per cent, and following miscellaneous strains, 4 per cent.

These percentages, striking as they are, do not adequately express the differences observed at necropsy because one lesion found in an animal injected with a nonmyositis culture counts for as much in the table as many lesions in an animal following the injection of the myositis strains.

In two cases in which there was a history of peridental symptoms (Cases 567 and 913) lesions of pulps of teeth or adjacent periosteum occurred in 50 per cent of thirty-five animals injected. The remarkable tendency of these strains to localize electively (Table 4) was paralleled in individual instances in which localization in animals was not only in muscles, but chiefly in the same group of muscles, as was noted in the patient. Thus in myositis of the gluteus muscles (Case 621) the localization was chiefly in this group. In two cases of cervical myositis (Cases 567 and 909) the chief localization occurred in the muscles of the neck. In two cases of intercostal myositis the localization was almost limited to the intercostal muscles, and in one case this was true in two sets of experiments (Fig. 349, III and IV). In the case of lumbar myositis (Case 624) the lesions in the rabbits were chiefly in the lumbar muscles (Fig. 349, II), a finding which supports the idea that infection may play a part in the etiology of chronic lumbago. In Case 913, in which the chief complaint was referable to the periarticular structures of the right knee, the striking localization in animals occurred around the knee joints (Fig. 357, IV). The lesions in the muscles of the animals injected with the bacteria from the myositis-neuritis group were frequently situated around nerves (Figs. 349, I, III and Fig. 350, I), and the lesions in nerves independent of muscle lesions sometimes corresponded to those involved in the patient. This was particularly true in Case 567 (Table 3), in which there were recurring attacks of facial neuralgia due to pulpitis and dental neuritis, and cervical myositis. The affinity of the slightly hemolyzing streptococcus isolated from the foul dental pulp and the excised muscles of the neck for dental pulps and dental nerves, and muscles of the neck, was so marked that lesions in these structures developed even after intraperitoneal injection. Besides lesions in muscles, arrhythmia of the heart, with lesions in the bundle of His and in the myocardium, developed in animals following the intravenous injection of streptococcus

from the pyorrheal pockets in Case 601, the patient who had had repeated attacks of muscular rheumatism and who was suffering from attacks of syncope due to a damaged His bundle and impaired myocardial conduction. Localization in muscles occurred in experiments performed during repeated attacks in some patients; for example, three times each in Cases 622 and 912, and five times in Case 1035. In one patient (Case 912) localization in muscles of animals occurred as the chief lesion during each of three widely separated attacks of acute localized myositis. Lesions in the gallbladder, myocardium, and pericardium, without muscle lesions, were produced during an attack of cholecystitis and pericarditis, with dilatation of the heart, and lesions in the stomach or duodenum developed in the animals injected during two attacks of indigestion. There were few or no lesions in the animals injected in the same way while the patient was free from symptoms on three widely separated occasions.

The strains from generalized myositis tended to produce numerous small lesions in many muscles, sometimes thousands of lesions, while those from localized myositis tended to produce a few localized areas of muscle involvement.

The objection which has been raised regarding dosage has been met not only by injecting smaller doses of cultures, but by directly injecting salt solution suspensions of the small number of bacteria in the pus expressed from tonsils. Indeed, some of the most specific localizations occurred in these experiments. It was thought worth while, therefore, to summarize the results obtained by injecting the small doses of the bacteria which had grown in the focus itself.

Lesions in muscles developed in all of fourteen rabbits injected with the pus from five patients in the uncomplicated myositis group. Two rabbits developed arthritis, and one rabbit had hemorrhage of the stomach in addition. Of the fifteen rabbits injected with the tonsil pus from nine patients in the myositis and arthritis group, fourteen developed lesions in the muscles, ten in the joints, two in the stomach, two in the myocardium, and one in the endocardium. Of the six rabbits injected with the tonsil pus from five patients in the myositis and neuritis group, five developed lesions in the skeletal muscles, one in the stomach, two in the myocardium, and three in the nerves. Thus, of the total of thirty-five rabbits injected, thirty-three (94 per cent) had lesions in muscles. The results obtained following injection of the tonsil pus from twelve persons who were well at the time or who had

some ailment not attributable to infection were in sharp contrast. Of the twenty-four rabbits injected, only three (12.5 per cent) had lesions in muscles, and one rabbit had hemorrhages of the stomach.

The virulence of the bacteria injected was of a low order. Of a total of 202 animals injected (168 rabbits, seventeen dogs, nine guinea pigs, seven mice, and one monkey) only forty-six died; 156 were anesthetized for examination. The results of cultures of the blood made

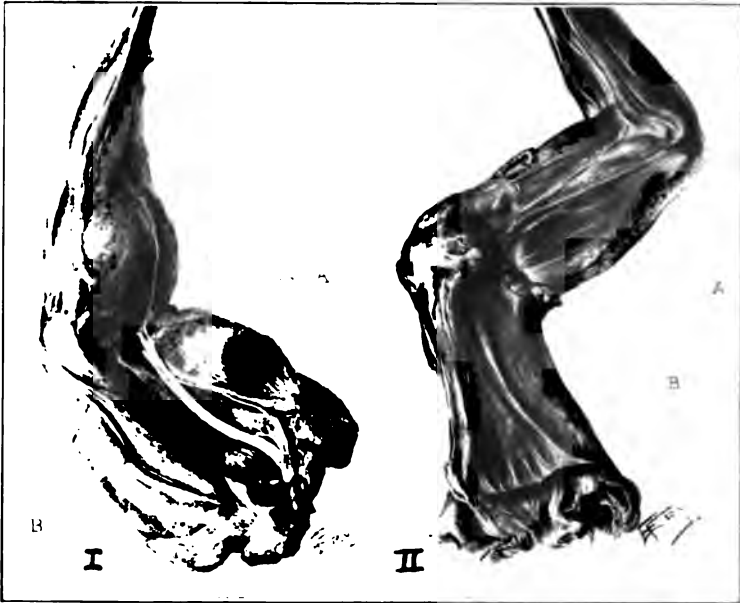


FIG. 348.—(I) Numerous small hemorrhagic lesions in the muscles of the hind leg of a rabbit forty-eight hours after injection of the primary culture of the streptococcus from the tonsils in a case of acute cervical and intercostal myositis (Case 909). (II) Numerous whitish necrotic lesions of the muscles of the foreleg and shoulder of a rabbit eight days after injection with the streptococcus from the tonsils after one animal passage in a case of marked but chronic myositis (Case 904).

at necropsy were recorded in 144 instances. In eighty-four no growth was obtained; sixty cultures were positive. Streptococcus was found in forty-five, staphylococcus in nine, colon bacillus in eight, and gram-staining bacillus in five. In most instances the cultures were pure, although mixtures of streptococcus and staphylococcus were found occasionally. Cultures of the blood of the animals that were sacrificed remained sterile in 62 per cent and showed growth in 38 per cent.

The blood of the animals that died showed growth in 54 per cent and remained sterile in 46 per cent. The number of colonies of streptococci on blood-agar plates in the positive cultures was relatively small. Often no growth occurred on aërobic plates when the deep broth cultures were positive. This was true even though the amount of blood inoculated was comparable in the two mediums. The oxygen sensitiveness was found also in the strains of streptococci isolated from the lesions in the muscles. Control culture of blood, and of various tissues without lesions, including normal muscles, were often sterile when cultures from the lesions in the muscles revealed streptococci. But even the lesions resulting from a single injection tended to become sterile so that cultures had to be made soon after injection, preferably in from twelve to forty-eight hours, in order to demonstrate the presence of living bacteria.

DESCRIPTION OF SYMPTOMS AND LESIONS IN ANIMALS

The animals injected with streptococci from the patients with generalized myositis usually developed numerous widely disseminated lesions, while those injected with strains from patients with localized areas of myositis usually developed only localized lesions in the muscles. The former often presented quite characteristic symptoms from which the existence of myositis was frequently predicted. The muscles appeared tender to touch. The animals sat around quietly, with ruffled fur, sometimes resting the nose on the floor of the cage. They were disinclined to move and when made to do so, walked about as if muscular effort caused pain and discomfort. They lost markedly in weight and often became very weak. The rabbits showing only localized lesions were usually free from demonstrable symptoms, and lost little or no weight. In some instances in both groups of animals, however, the discomfort from muscular effort noted during life could not be explained satisfactorily by the few gross lesions which were found in the muscles after death. In these animals, lesions of nerves, or hemorrhagic areas of muscles or fascia surrounding nerves were often demonstrable (Fig. 349, I, III and Fig. 350, I, II).

The lesions were of two main types. One type consisted of numerous small linear or oblong hemorrhages (Fig. 348, I); the other, of equally numerous small linear, grayish white, necrotic streaks (Fig. 348, II). The former was, in general, the early stage of the latter, and both types were often present in the same animal in varying propor-

tions. The time when the hemorrhagic lesions became necrotic varied greatly, depending to some extent on the size of the dose injected, but most of all on the strain of streptococcus. Following the injection of some strains only necrotic areas were found even as early as twenty-four hours after injection; with other strains only hemorrhagic areas were found, and these often disappeared without becoming necrotic. The lesions obtained with staphylococci were quite different. Suppuration frequently occurred, and the surrounding edema and hyper-

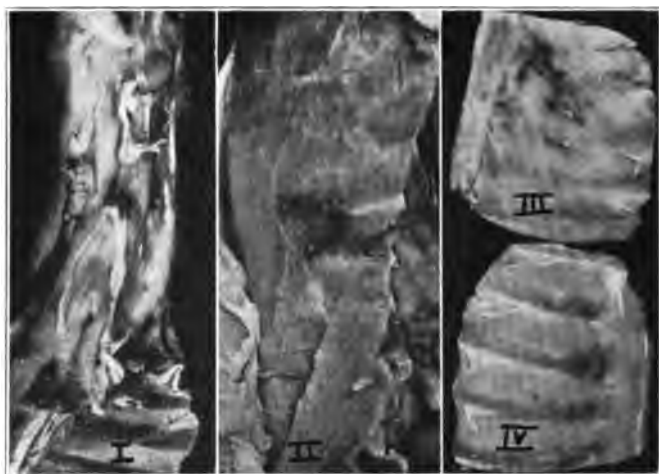


FIG. 349.—(I) Hemorrhagic lesions in the muscles of the neck surrounding the exit of the fifth cervical nerve of the rabbit injected with the tonsil pus in Case 909. (II) Localized area of hemorrhage, edema, and infiltration of the muscles of the lumbar region in a rabbit injected with the streptococcus from the tonsils in a case of lumbar myositis (Case 624). (III) Hemorrhagic lesions in the external aspect of the muscles of the upper thorax, especially around the exit of the small nerve trunks, in a rabbit injected with the streptococcus isolated from the mucopurulent discharge from the nose of a man at the time of an attack of intercostal myositis. (IV) Hemorrhagic lesions in the internal intercostal muscles of the thorax in the rabbit referred to in III.

emia were more pronounced. The small hemorrhagic and necrotic lesions due to streptococci were often widely distributed throughout the skeletal muscles. They were nearly always more numerous in the flat muscles of the trunk, along the tendinous partitions, and in the tendinous ends of the muscles of the extremities. This picture was in sharp contrast to that following the injection of the strains from cases of localized myositis. Here disseminated lesions rarely developed, but instead localized areas of large and small hemorrhages, associated early

with little or no edema and infiltration, while later the edema, infiltration, and necrosis often became marked. Softening with pus formation was rare, but it occurred more often in the animals with large localized lesions than in those with small, widely disseminated lesions.

The microscopic findings were very interesting. The lesions usually developed between the muscle fibers and consisted first of extravasation of red blood corpuscles, dilatation of adjacent capillaries, and swelling of the muscle fibers with disappearance of the transverse striations as



FIG. 350.—(I) Hemorrhagic lesions in the muscles, surrounding the nerve trunks, of the under surface of the scapula and thorax of a rabbit injected with the streptococcus from infected teeth of a man having myalgia, especially of the chest and shoulder muscles (Case 923). (II) Hemorrhagic lesions in the internal aspect of the muscles of the hind leg along the tendinous partition and adjacent nerve trunk in a rabbit injected with the streptococcus from the tonsils of a neurasthenic young woman at the time of localized myalgic pains of the thorax, and numbness of the right arm (Case 571).

interstitial edema and leukocytic infiltration became manifest. Later, in the larger lesions the muscle fibers became fragmented and necrotic as leukocytes and other cells became numerous. The amount of cellular infiltration varied from large areas of infiltration (Fig. 353, I) to the aggregation of only a few cells between the muscle fibers (Fig. 353, II). Deposits of calcium salts occurred relatively early in the necrotic areas (Fig. 354, II), especially in the rabbits after the injection of the streptococcus isolated from the muscle in the case of calcifying myositis (Fig. 354, I). A marked deposit of calcium was noted as early as forty-

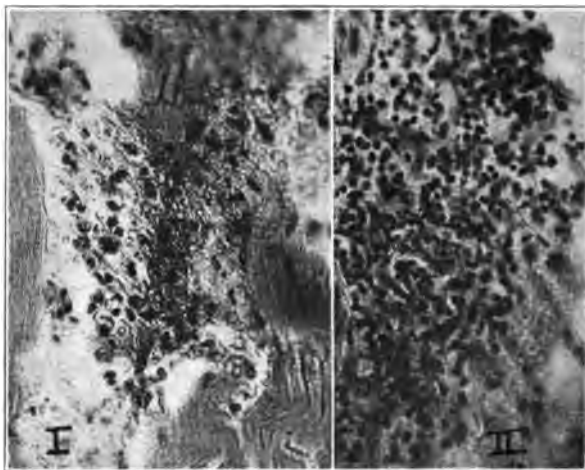


FIG. 351.—(I) Hemorrhage and leukocytic infiltration within and between the muscle fibers in the excised muscle in a case of acute rheumatic myositis in man. Hematoxylin and eosin ($\times 200$). (II) Marked leukocytic infiltration in an excised section of muscle from the forearm of a patient with acute localized myositis. Hematoxylin and eosin ($\times 200$).

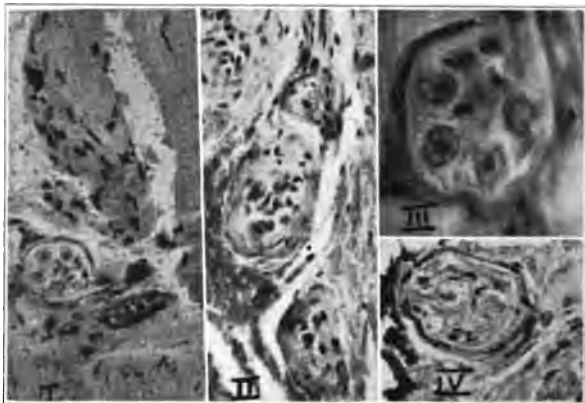


FIG. 352.—(I) Section showing slight round-cell infiltration and complete plugging of a small blood vessel from hyperplasia of endothelial cells in the tendinous portion of an excised section of muscle in a case of chronic myositis and arthritis deformans. Hematoxylin and eosin ($\times 200$). (II) Obliteration of blood vessels in the tendinous end of a muscle in a case of chronic myositis and peri-arthritis. Hematoxylin and eosin ($\times 200$). (III) Obliteration of blood vessels from hyperplasia of endothelial cells in a muscle in a case of chronic myositis and arthritis. Hematoxylin and eosin ($\times 700$). (IV) Obliteration of a blood vessel in another field of section shown in I. Hematoxylin and eosin ($\times 200$).

eight hours after the injection of this strain; whereas, after the injection of other strains, where necrotic lesions were fewer, little or no calcification was noted. Areas of necrosis of considerable size appeared necessary for the deposit of calcium, a fact which seems to support Wells' theory of calcification. There was usually no difficulty in demonstrating the organism in the lesions soon after injection (Figs. 355, II;

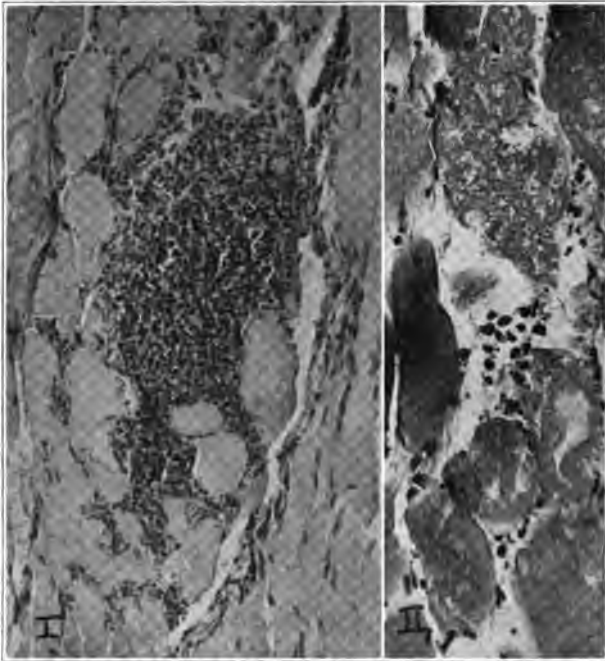


FIG. 353.—(I) Section of a whitish lesion, like those shown in Figure 348 (I), in the muscle of a rabbit injected with the streptococcus from the tonsils in Case 904. Hematoxylin and eosin ($\times 100$). (II) Slight leukocytic infiltration and edema between the muscle fibers and the myocardium of a rabbit injected with streptococcus from the tonsils, after one animal passage, in a case of myositis and myocarditis (Case 601). Hematoxylin and eosin ($\times 200$).

356, III; 357, III and IV), but later this was often difficult and sometimes impossible. The microscopic changes in the human muscles in acute myositis (Fig. 351, I and II) were similar to those produced experimentally. They consisted of extravasation of red blood corpuscles, interstitial edema, cellular infiltration, swelling and necrosis of the muscle fibers, with disappearance of transverse striations. The

demonstration of streptococci was also possible (Fig. 357, I and II). The whole picture parallels quite closely the description by Körmöczy of the microscopic findings in muscles in a patient who died of acute myositis caused by a streptococcus.

The sections of atrophic and tender muscles and periarticular structures in chronic myositis and arthritis showed relatively little cellular infiltration (Fig. 352, I), but showed a marked swelling of the endothelium and sometimes complete plugging of the blood vessels from

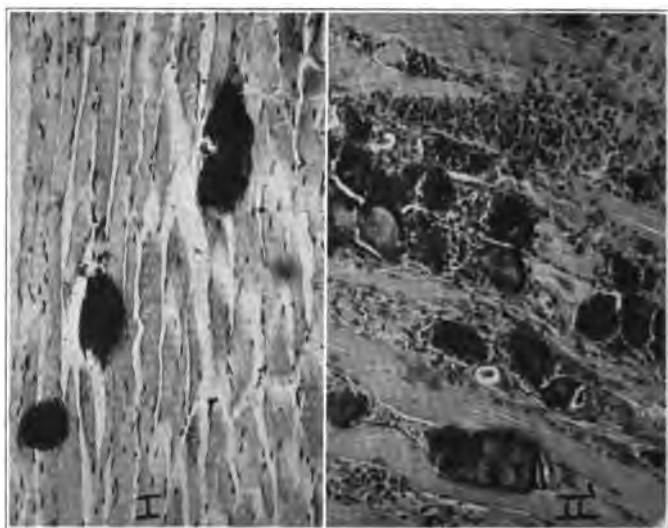


FIG. 354.—(I) Section of muscle in a rabbit six days after injection of streptococcus from the muscle in the case of calcifying myositis (Case 130). Note the marked deposit of calcium in sharply circumscribed areas. Hematoxylin and eosin ($\times 80$). (II) Section of muscle of rabbits shown in Figure 348 (I). Note the disintegration of the muscle fibers, leukocytic infiltration, and moderate deposit of calcium in the necrotic areas. Hematoxylin and eosin ($\times 100$).

proliferation of endothelial cells (Fig. 352, I, II, III, and IV). Streptococci have been isolated by cultural methods from these excised tissues and demonstrated in the endothelial cells, but not without prolonged search.

Owing to these findings it was thought that a study of the changes in the blood vessels in the muscles of rabbits showing lesions might throw some light on the mechanism involved in the localization of the bacteria and the production of the lesions. The changes in the small blood vessels were found to consist of two quite distinct types, aggrega-

tion of leukocytes within the lumen (Fig. 355, I), and more rarely in the perivascular lymph spaces. This occurred commonly after the injection of strains from patients with acute myositis, who recover promptly. The demonstration of bacteria in the wall of these vessels was not accomplished, but in a few instances diplococci were found within the leukocytes. The small vessels following injection of the

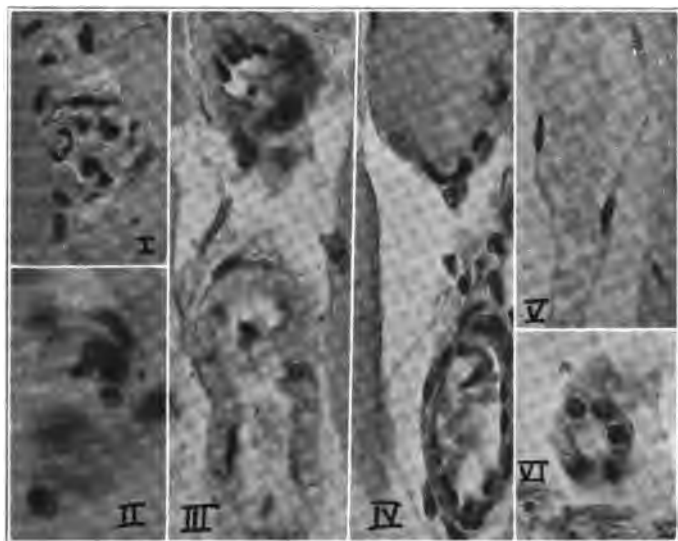


FIG. 355.—(I) Cross-section of capillary showing aggregation of leukocytes within the lumen adjacent to the lesions in the muscle shown in Figure 353 (I). Hematoxylin and eosin ($\times 500$). (II) Diplococcus in the wall of a capillary showing marked swelling of the endothelial cells in the muscle of a rabbit one day after five daily injections of liquor formaldehyd-killed streptococci from Case 904 after one animal passage. Giemsa ($\times 1,000$). (III) Cross-section of an arteriole and a venule in the muscle adjacent to lesions in rabbit shown in Figure 348 (I). Note the marked swelling of the endothelial cells. Hematoxylin and eosin ($\times 500$). (IV) and (V) Sections of normal arteriole, venule, and capillary of muscle in (III), but remote from lesions. Note the absence of swelling of the endothelial cells. Hematoxylin and eosin ($\times 500$). (VI) Marked swelling of the endothelial cells in a capillary in the muscles of rabbit shown in Figure 348 (I). Hematoxylin and eosin ($\times 500$).

strains from chronic generalized myositis, especially after repeated injections of the dead organisms, presented a very different picture. There were few or no leukocytes even soon after injection. The reaction appeared to be chiefly endothelial. The endothelial cells lining the vessels were often markedly swollen (Fig. 355, III and VI), and diplococci were sometimes demonstrable (Fig. 355, II). Proliferation of

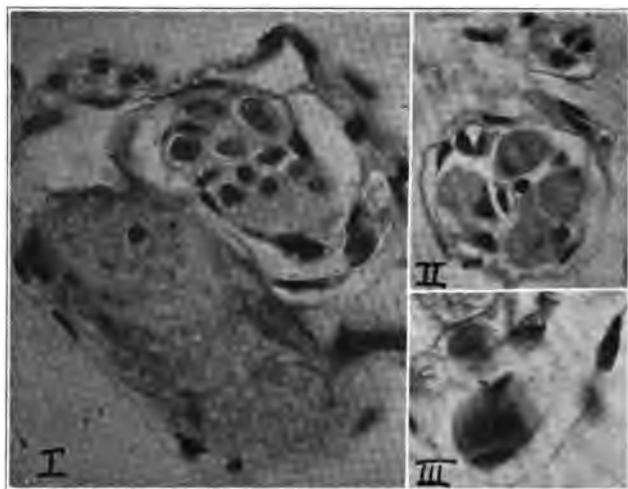


FIG. 356.—(I) Cross-section of arteriole, venule, and nerve fiber of a rabbit one day after five daily injections of liquor formaldehyd-killed streptococci from Case 904. Note the marked proliferation of the endothelial cells in the arteriole. Hematoxylin and eosin ($\times 500$). (II) Cross-section of nerve fiber and terminal sensory organ in muscle of rabbit referred to in (I). Hematoxylin and eosin ($\times 500$). (III) Diplococcus in partial focus within the swollen cells of the sensory organ shown in (II). Giemsa ($\times 1,000$).

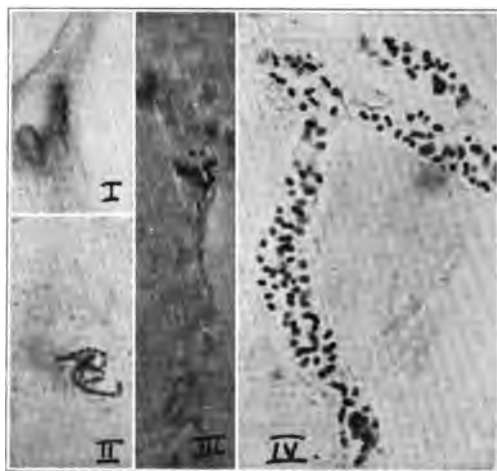


FIG. 357.—(I) Chain of two diplococci in the section of human muscle shown in Figure 351 (I). Gram-Weigert ($\times 1000$). (II) Chain of streptococci in the area of leukocytic infiltration shown in Figure 351 (II). Gram-Weigert ($\times 1000$). (III) Diplococci in the area of leukocytic infiltration shown in Figure 353 (I). Gram-Weigert ($\times 1000$). (IV) Large number of gram-positive diplococci in capillaries of a hemorrhagic area in the quadriceps tendon of a rabbit two days after injection with the streptococcus from the tonsils in a case of periarthrits and myositis (Case 913). Gram-Weigert ($\times 1000$).

endothelial cells containing deeply staining nuclei occurred in some arterioles, especially in prolonged experiments where repeated injections of liquor formaldehyd-killed streptococci were given (Fig. 356, I). The changes noted in the small blood vessels in response to the intravenous injection of bacteria recall the peculiar behavior of small blood vessels noted by Hooker in the ear of the cat during life following the injection of hystamin and other substances.

During the microscopic study attention became directed to what at first were thought to be cross sections of blood vessels in which the lumen was filled with endothelial cells, but which on closer study were considered to be peripheral sensory end organs (Fig. 356, II). The cells of these differed from swollen endothelial cells in being more nearly round, and in that the nuclei were usually situated to one side. After prolonged search undoubted diplococci were found in these highly specialized nerve cells (Fig. 356, III).

LOCALIZATION OF DEAD STREPTOCOCCI FROM MYOSITIS

It was thought that the injection of the dead bacteria as a control might throw light on the mechanism of the production of myositis. Particularly suitable cultures, those in which the living organisms produced marked lesions in muscles, were used. Liquor formaldehyd was selected as the most desirable agent with which to kill the streptococci. One of us had found previously that liquor formaldehyd-killed pneumococci failed to autolyze. The agglutinability of typhoid bacilli killed with liquor formaldehyd remains unchanged for a long time.

After growing the streptococci in tall columns of ascites-glucose broth for from eighteen to twenty-four hours 0.5 c.c. of formalin (40 per cent strength) were added for each 100 c.c. of the culture. This was thoroughly mixed and allowed to stand at room temperature for twenty-four hours, when sterility tests were made. The dead bacteria were then removed by centrifugation and the sediment, which was drained dry, was suspended in 0.85 per cent salt solution so that 1 c.c. contained the growth from 15 c.c. of the broth culture. From 0.5 to 10 c.c. of this suspension, representing the growth of from 7.5 to 150 c.c. of broth, were injected into rabbits weighing from 1050 to 2150 gm. In most of these animals repeated daily injections, as high as six, were given. The animals were sacrificed usually in from one to ten days after the last injection. The effect of dead streptococci from five cases of myositis (Cases 130, 369, 567, 601, and 904) was studied in

eleven rabbits. Lesions similar in location and distribution to those obtained with the corresponding live bacteria were obtained in eight animals following injection of the strains from four cases. No lesions were found in the other three, all of which were injected with small doses.

In the case of dental neuritis and cervical myositis (Case 567) the three rabbits had lesions in the flat and tendinous partitions of muscles and dental pulps. One of these was injected once with the dead streptococci from the primary growth of the excised muscle, one on four occasions with this strain in the second culture from a single colony on blood-agar, and one with the dead streptococci from the primary culture from the infected tooth pulp. The Berkefeld filtrate of the supernatant broth was injected intravenously daily into one rabbit for three days in 12 c.c. doses. It remained well and was anesthetized for examination on the fourth day. No lesions were found. The lesions following the injection of the dead organisms were less numerous and smaller than those following the injection with the corresponding live culture, even though the dose of the dead bacteria was much larger. The lesions consisted of small hemorrhages with little edema and infiltration. In some areas dilatation of blood vessels was found microscopically, in others, constriction, with swelling of endothelial cells. In some instances the vessels were partially or completely filled with endothelial cells. Intravascular and interstitial leukocytic reactions were slight or absent. The changes in the muscle fibers consisted chiefly of swelling, disappearance of the striations, occasionally of fragmentation, and at times of beginning fatty degeneration.

The demonstration of the streptococci in the tissues was difficult. Most of the bacterial cells were disintegrating and had lost much of the Gram stain. Unmistakable diplococci, sometimes in short chains, were found within swollen endothelial cells lining the small blood vessels in the areas of hemorrhage (Fig. 355, II), between the muscle fibers, and within what appeared to be sensory end organs (Fig. 356, III).

DISCUSSION AND SUMMARY

Localized infections around teeth and in tonsils were demonstrably present in nearly all of the twenty-eight patients studied. Improvement in symptoms, often striking, occurred in all but one of the twenty-five patients from whom foci were removed. In the twenty-four patients in whom improvement did occur the focus was shown to contain bacteria which tended to produce lesions in the muscles of animals, while

in the one patient in whom improvement did not occur the bacteria failed to produce lesions. In some patients recurrence of myositis or only partial recovery was found to be due to defective tonsillectomies, to inadequate dental operations, to failure in recognizing the existence of foci in teeth, or to the development of new localized areas of infection. Therefore, localized infections in tonsils, teeth, and elsewhere in the patients studied appeared to play an important part not only in the etiology of pure myositis, but also in associated conditions, such as myositis and arthritis, myositis and neuritis, nontraumatic lumbago, and myocardial degeneration. In the light of these facts foci of infection apparently not only make a forced relationship between the bacteria and their products and the mechanism of resistance of the host, but, it would seem, afford the conditions favorable for the micro-organism to acquire peculiar infecting powers.

The elective affinity of the streptococci from these localized infections was so marked that the organisms not only tended to localize and produce lesions in muscles, but the location of the lesions often approximated that noted in the patient. When the affection of other structures, such as joints and nerves, appeared as a secondary factor in the patient's symptomatology, lesions were also found in these structures in the injected animals, and the percentage of animals showing them was proportionately less than the percentage of animals showing muscle lesions. In pregnant rabbits localization was found to occur not only in the muscles of the parent rabbit but also in the fetuses.

The localization in the myocardium, especially in the bundle of His, and the concomitant development of arrhythmia of the heart following the injection of cultures from pyorrheal pockets in the case of impaired myocardial conduction is another striking example of the extreme specificity of these strains for certain tissues. This narrow specificity for certain tissues is in keeping with the fact that myositis occurs during certain epidemics of respiratory infections, and with the striking example of elective localization in a wide-spread epidemic of myositis reported by Curschmann, in which the muscles of the neck were chiefly involved.

The streptococcus from myositis did not differ greatly in morphology, cultural character, and staining reactions from those isolated in other diseases studied, and the reasons for the myositis strains possessing affinity for muscles, and the other strains for the respective other tissues or organs are still obscure. The fact, however, that the killed

streptococci from myositis localized in muscles, as did the live organism, indicates that the property (chemical structure, electrical charge, perhaps) upon which this depends resides within the bacterial cell. The observation that the dead streptococci revealed evidence of disintegration as lesions in the muscles developed suggests that the poisons which cause the symptoms and lesions in myositis are either preformed in the bacterial cells or are formed as they disintegrate. The latter view is strongly supported by the experiments performed by one of us²¹ some years ago, in which it was shown that when streptococci and other bacteria undergo digestion highly poisonous substances of a similar nature, regardless of the species, are formed during the early stages of proteolysis and that these disappear as proteolysis proceeds to a further point. According to the results of these experiments and those of Zinsser and his co-workers, in which toxic substances are formed similar in their effects, irrespective of the species of microorganism, the localizing power of bacteria rather than specific poisons becomes a factor of first importance in the etiology of myositis, as indeed it may be of other diseases.

The retention of the peculiar affinity during the killing process of those streptococci is in keeping with the fact discovered by Marchand, that opposition of virulent organisms to phagocytosis is not destroyed by heat, and to the observation by one of us¹⁷ that the resistance to phagocytosis of virulent pneumococci is due to an extractable substance, "virulin." The fact that the streptococci having affinity for the muscles in these cases are culturally dissimilar does not argue against their having etiologic relationship. The symptoms and the course of the disease are so variable as to suggest their not being due to a specific microorganism. The streptococci from the joints of patients with acute rheumatic fever having elective affinity, it will be recalled, were also dissimilar.²¹

The finding of the *Staphylococcus aureus* in the tonsils in Case 536 having elective affinity for muscles indicates that this organism may be the cause of mild myositis, just as Martinotti and Schmitz have shown this to be so in one case each of acute polymyositis, in which this organism was isolated from the muscle lesions and was found to have elective affinity for the muscles of animals, producing lesions in muscles almost to the exclusion of lesions in other organs.

From the microscopic study of sections of muscles in chronic myositis and arthritis deformans, and of those in animals following repeated

injections of these strains, a most interesting mechanism in the production of the lesions has been discovered. Evidence has been obtained of why cure in these chronic affections is so difficult, and the reason massage and applications of heat are such valuable agents in their treatment. The reaction in these very chronic conditions is not leukocytic, but mainly mononuclear and endothelial. The endothelial cells lining the small blood vessels become extremely swollen, proliferate, and, in consequence, the lumen of vessels, including arterioles, becomes partially or completely obstructed. The supply of available oxygen is thus lowered and the growth of the organisms favored, for it has been found that the streptococci from the lesions in muscles are very sensitive to oxygen. The common occurrence of spontaneous and experimental lesions in flat muscles or in the tendinous ends where the normal blood supply, and, consequently, the supply of available oxygen in response to insult are relatively low would seem to be due to the same cause.

Our success in isolating the strains and in reproducing the lesions is due, we feel, in large part to the use of culture mediums (tall columns of glucose-brain broth or ascites broth) which afford a gradient of oxygen pressure, to the injection of animals as soon as abundant growth occurred, usually within twenty-four hours, and to the painstaking effort made to obtain bacteria from the depths of foci of infection.

Bacteria having specific affinity for muscles have been demonstrated regularly in the foci of infection and, in some instances, on the free surface of mucous membrane and in excised muscles in cases of myositis in man. With these organisms the disease has been reproduced, the organism isolated from the experimental lesions, and demonstrated in them, and myositis again produced on reinjection. The lesions in animals, in general, corresponded in their severity and distribution to those present in the patient from whom the strains were isolated, and in that they were usually nonsuppurative in character. The number of lesions was often in proportion to the size of the dose. The conclusion, therefore, may be drawn that myositis, including even the mild transient affections of muscles, is caused in the main by lodgment and growth of bacteria, usually streptococci, which have elective affinity for muscle tissue.

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DIAPHRAGMATIC SPASMS IN ANIMALS PRODUCED WITH A STREPTOCOCCUS FROM EPIDEMIC HICCUP. PRELIMINARY REPORT*

EDWARD C. ROSENOW

The etiology of epidemic hiccup is quite obscure. Its occurrence at times in epidemic proportions suggests a microbic origin. Epidemiologic and clinical facts suggest that the cause of the condition is similar to the cause of epidemic encephalitis. Hiccup frequently occurs in cases of epidemic encephalitis. The two diseases occur simultaneously in many localities and over wide-spread areas of population.¹ Epidemic encephalitis has occurred in persons who have had recent attacks of uncontrollable hiccup, as well as after prolonged contact with patients with epidemic hiccup.^{2, 3}

Mindful of the extreme specificity of bacteria isolated from various foci of infection in other diseases I have studied, I thought that such areas might harbor the etiologic agent of epidemic hiccup. Three patients with prolonged uncontrollable hiccup have been studied from this standpoint. The material was obtained on the second day of a three-day attack from the first patient; from the second, on the seventh day of a recurrence three weeks after an initial attack lasting ten days; from the third, on the fifth day of an attack of seven days' duration. These patients were well otherwise, and all recovered.

The tonsils appeared normal on inspection, but a considerable amount of pus was expressed from each, and a suspension of the pus obtained was made in 2 c.c. of salt solution. Washings from the nasopharynx and suspensions of pus from pyorrhea pockets were also studied. From these suspensions blood-agar plate and glucose-brain broth cultures were made. Animals were inoculated directly with the suspensions in salt solution, and with the cultures in glucose-brain broth. From 0.2 to 0.01 c.c. of the salt solution suspension, and from 0.2 to 0.0001 c.c.

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of the culture in glucose-brain broth were injected intracerebrally into rabbits and monkeys.

After a period of incubation lasting from one to seven days, depending largely on the size of the dose and the virulence of the strain, a remarkable train of symptoms developed, in which rhythmic clonic spasms of the diaphragm were the striking feature (Fig. 358). The spasms of the diaphragm varied greatly in severity and duration. In some animals the spasms were mild and were noted for short periods at one or more intervals only, and recovery was the rule. In others they were intense, associated with hiccup, and continued with little interruption for many hours, often to the point of complete exhaustion of the animals. The spasms were temporarily controlled by the administration of ether; they were controlled for some hours by depressants of the

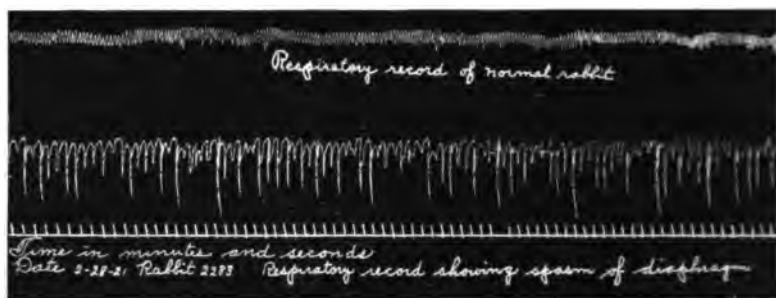


FIG. 358.—Respiratory record of Rabbit 2283, showing spasms of the diaphragm, and respiratory record of a normal rabbit.

respiratory center, such as heroin and morphin, and for short intervals by uniform, quite firm pressure around the abdomen at the level of the diaphragm. All the animals in which the spasms became marked died. Spasms of the diaphragm were produced in rabbits, monkeys, dogs, and guinea pigs.

The intracerebral injections were the most successful, although spasms of the diaphragm occurred following intravenous and intratracheal injections, and following packing of the nose with gauze soaked in the cultures, and the introduction of the organism into teeth from which the pulp was removed. Control experiments with material from similar sources were negative.

The gross lesions found at necropsy were relatively slight. The spinal fluid was usually clear or only moderately turbid, and increased in amount. The mononuclear cells usually predominated. The vessels

of the meninges were congested. The pia over the base of the brain, pons, medulla, and more rarely over the cerebellum was edematous and slightly cloudy. Usually no gross hemorrhages were found in brain or cord. Occasionally circumscribed areas of hemorrhage and infiltration were found in the cortex, especially in the lower Rolandic area, in the medulla, and in the cervical cord at the point of exit of the anterior roots of the upper cervical nerves. There was seldom any mark at the point of injection in the right frontal lobe. Suppurative meningitis

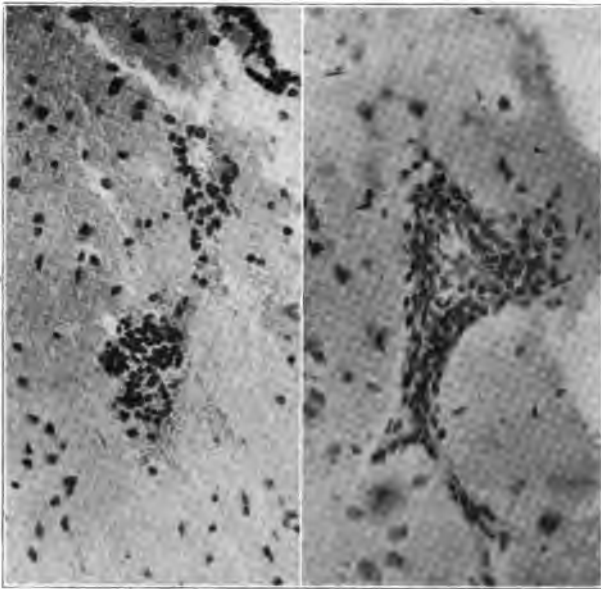


FIG. 359.

FIG. 360.

FIG. 359.—Circumscribed and perivascular round-cell infiltration in brain of Rabbit 2341 near the right lateral ventricle; hematoxylin and eosin ($\times 200$).

FIG. 360.—Perivascular round-cell infiltration in brain of Rabbit 2346; hematoxylin and eosin ($\times 200$).

was rare. No lesions were found in the phrenic nerves, and only occasionally hemorrhages in the diaphragm. The microscopic findings in the main consisted of circumscribed areas of hemorrhage, necrosis, and leukocytic and round-cell infiltrations, usually surrounding blood vessels; the type of lesion varied according to the duration of the experiment, although round-cell infiltration usually predominated even in the experiments of short duration (Figs. 359, 360, and 361). The lesions were most marked in the basal ganglions, in the walls of the

ventricles (Fig. 359), and in the gray matter of the cortex and medulla. Bacteria were easily demonstrable in the more acute lesions, but in the more chronic lesions they were fewer and could be found only after prolonged search. In animals that had recovered and were chloroformed, and in those that died late, it was often impossible to demonstrate the bacteria in the areas of round-cell perivascular infiltration.

The organism isolated from the brain and spinal fluid of the animals that developed hiccup following injections of material from each

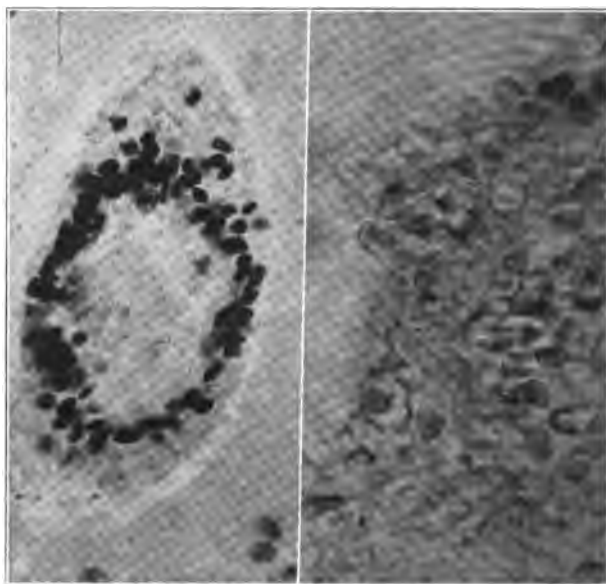


FIG. 361.

FIG. 362.

FIG. 361.—Adventitial round-cell infiltration and perivascular hemorrhage in the base of the brain of Rabbit 2341; hematoxylin and eosin ($\times 500$).

FIG. 362.—Diplococci in the area of perivascular hemorrhage shown in Figure 361; Gram-Weigert ($\times 1,000$).

of the three patients was a gram-positive, nonencapsulated diplococcus, which produced small, nonadherent greenish colonies on blood-agar plates, and short chains in liquid mediums. The freshly isolated cultures, especially those from the first patient, tended to produce, on lightly seeded plates, rather large, slightly elevated, often umbilicated colonies. The growth in glucose-brain broth and ascites-glucose broth was rapid and diffuse. Diplococci predominated in the tissues (Fig. 362), although short chains of from two to four diplococci were found.

In young aerobic cultures the organism was quite uniform in size and shape, resembling nonencapsulated pneumococci. In ascites tissue fluid it grew more slowly and varied greatly in size and shape, resembling the streptococcus from poliomyelitis. The strain from the second patient fermented inulin and was bile soluble; the strains from the other two did not ferment inulin and were not bile soluble. Cultures from the blood and other tissues were usually sterile or contained few bacteria as compared with the brain and cord. The freshly isolated strains from the first and third patients were agglutinated by an anti-streptococcus serum prepared with a similar streptococcus isolated from a patient with lethargic encephalitis, but none were agglutinated by antihemolytic streptococcus serum, by the antistreptococcus serum prepared from one strain of the green-producing streptococcus found so commonly in influenza, or by the type pneumococcus serum.

Filtrates of the nasopharyngeal washings, of suspensions from the pus, from tonsils, and teeth of the patients, of emulsions of brain and cord from animals that died with typical symptoms, and of cultures which proved sterile by cultural methods, gave negative results following intracerebral inoculation.

Aerobic cultivation on blood agar destroyed promptly the specificity of the strains, but by making frequent transfers into tall tubes of warmed glucose-brain broth, from four to six times in each twenty-four hours, specific agglutinating and infecting power was preserved for many generations. Thus the strain from the first patient produced typical symptoms and lesions in a series of animals in the seventh, thirty-third, thirty-seventh, and fiftieth culture generations, while in the seventy-third generation suppurative meningitis developed instead.

The close relationship between epidemic hiccup and epidemic lethargic encephalitis, noted clinically, was suggested not only by the similarity of these strains to those I have isolated in encephalitis (to be published) but also by the results in the animal experiments. It was noted that after several animal passages fewer animals developed hiccup, and a larger proportion developed lethargic and other symptoms of encephalitis.

PROTOCOLS ILLUSTRATING IN GENERAL THE RESULTS OBTAINED

Experiment 1.—Rabbit 2283, weighing 1,380 gm., was injected intracerebrally February 22, 1921, with 0.1 c.c. of the salt solution suspension of the pus expressed from the tonsil of the first patient studied. The rabbit appeared well until February 27, when it

was unusually quiet, disinclined to move, and was somewhat shaky when made to hop around. February 28 at 8 a.m., it was found lying on its side, and having repeated sudden spasms of the diaphragm of varying intensity. The interval between the spasms varied from one to four seconds (Fig. 308). With each of the more severe spasms audible hiccup and clonic spasms of the muscles of the extremities and, at times, of the neck occurred. When the animal was lifted to a new position, or was turned to the opposite side and attempted to get on its feet, more generalized clonic spasms occurred. After it became quiet the spasms of the diaphragm recurred. For long intervals these spasms were unassociated with spasms of other muscles, although occasionally clonic spasms of the muscles of the extremities were noted. The animal was etherized at 5 p.m.

The cerebrospinal fluid was slightly turbid and increased in amount. The meninges were moderately congested; several areas of edema containing small punctate hemorrhages over the left lower Rolandic area, and small hemorrhages in the cervical cord opposite the anterior roots of the third and fourth cervical nerves on both sides were found. There were no lesions in the phrenic or vagus nerves, or in the diaphragm. Sections of the brain and medulla showed circumscribed, usually perivascular, areas of necrosis, and leukocytic and round-cell infiltration.

The cultures from the brain and cerebrospinal fluid contained large numbers of colonies of slightly green-producing streptococcus, those from the liver contained a few, while those from the blood, kidney, and spleen were negative.

Experiment 2.—Rabbit 2341, weighing 710 gm., was injected intracerebrally March 8, 1921, with 0.0001 c.c. of a three-hour culture of the organism isolated from Rabbit 2283 in the thirty-seventh culture generation. The animal remained well until March 12, when it was unusually quiet and disinclined to hop around. March 13 at 7 a.m., it sat about quietly, disinclined to move, and appeared uncomfortable; its fur was ruffled. At noon the animal was about the same, although it had become somewhat shaky and tremulous. At 2 p.m., it was found sitting in the cage, having repeated clonic spasms of the diaphragm, which it seemed to try to control by assuming various positions, such as stretching out its extremities and lying flat on its abdomen, and getting up and sitting in a humped position. At 4.30 p.m., it was found lying on its side in a relaxed condition, having repeated rhythmic sharp spasms of the diaphragm, in which audible hiccup occurred with the more severe spasms. At 5 p.m., it was found dead.

The cerebrospinal fluid was slightly turbid and increased in amount. There was no mark at the point of injection. The meninges were clear. A few small punctate subpial hemorrhages over the cortex in the lower half of the right Rolandic area, and hemorrhagic edema in the cord opposite the roots of the third, fourth, and fifth cervical nerves were found. There were no lesions in the phrenic or vagus nerves or in the diaphragm. Sections of the brain and medulla showed circumscribed and perivascular round-cell infiltration (Figs. 359 and 361).

The cultures from the brain and spinal fluid yielded a large number of colonies of green-producing streptococcus, and the blood yielded a few colonies.

Experiment 3.—Rabbit 2346, weighing 2,000 gm., was injected March 10, 1921, intracerebrally with 1.5 c.c. of the filtrate of the brain emulsion of two monkeys that developed hiccup following intracerebral inoculations with the strain from Rabbit 2283 after thirty-seven subcultures. The cultures in glucose-brain broth from this filtrate yielded the streptococcus. The rabbit was well until the evening of the day after the injection, when it appeared drowsy, responded slowly to stimuli, and rested its nose on the floor of the cage, in apparent sleep. At 10 p.m., the drowsiness and tardy response to stimuli had increased. Respirations were slow and the ears were held erect. March 12 at 7.30 a.m., the animal was found sitting quietly in the cage, apparently sound asleep. It was aroused with difficulty, but when thoroughly aroused it hopped around, but went directly

back into apparent deep sleep. At noon, the animal was about the same, and could be placed in different positions with little or no resistance. It was photographed, apparently asleep, in a sitting position, lying on its side, and on its back with extremities extended in the air. While being photographed it awakened sufficiently to lick its paws, and wash its nose and mouth, which were wet from saliva. It refused to eat carrot which was held to its mouth, but if pieces of carrot were placed in its mouth it masticated slowly for a short time and then apparently forgot to swallow, and the pieces partially masticated were held in its mouth for a long time. The respirations were slow. There were occasional twitchings of the eyelids, but no other spasms. The *tonus* of the muscles of the extremities was not noticeably increased. At 3 p.m., the condition of the animal was quite unchanged. It responded slowly to stimuli, and when awakened it lifted its head, opened its eyes, and then again promptly fell asleep. After considerable effort it was aroused sufficiently to drink water and eat oats. It stopped eating and drinking repeatedly, apparently falling asleep, and when prodded it would again eat and drink. At 9 p.m., the animal was found in exactly the same position in which it was left in the afternoon, apparently sound asleep, with slow respirations, ears erect, and eyes half closed. At this time it ate with apparent relish several mouthfuls of ground carrot, but goading was necessary, as it would repeatedly stop, apparently forgetting to swallow. A curious phenomenon was noted at this time. If the carrot was brought to the animal's mouth from the left side it paid no attention, but if brought from the right side it would eat. This was associated with a slow turning of the head to the right, even to the point of losing its balance. March 13 at 7.30 a.m., it was found sitting quietly in the cage, apparently sound asleep. With some effort it could be aroused sufficiently to eat ground carrot, but it repeatedly fell asleep and more quickly than the previous day. Repeatedly during the day it was found in apparent deep sleep; with considerable effort and prodding it could be awakened sufficiently to eat ground carrot, but it was apparently unable to open its mouth sufficiently to bite the carrot because of rigidity of the muscles of the jaw.

March 14, the animal was undoubtedly brighter. It took more notice of its surroundings, responded more quickly to stimuli, appeared hungry, and ate oats and ground carrot with a relish. Tremor of the muscles of the neck and moderate ataxia became apparent as the animal hopped around. While eating it still frequently forgot to masticate and swallow, and apparently fell asleep, but when aroused it would again eat. March 15, it was still quite sleepy, and distinct tremor of the head, repeated twitchings of the muscles of the upper part of the abdomen on the left side, and distinct ataxia were noted. It tended to lose its balance in reaching for the carrot on the side. During the following four days the animal apparently recovered completely and was chloroformed.

No gross lesions were found. The cerebrospinal fluid was increased in amount, but it was clear. Cultures from the brain, blood, and spinal fluid were negative. Sections showed perivascular round-cell infiltration in the base of the brain (Fig. 360), but no lesions in the cord.

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EFFICIENCY IN THE DIAGNOSIS OF NEOPLASMS*

WILLIAM C. MACCARTY

Questions have often been asked for the purpose of formulating a plan by which they may be answered, and the one which I am about to ask and shall attempt to answer is: "Have we, as a profession, reached our greatest efficiency in the clinical diagnosis of neoplasms?" We have spent a great amount of time and some money trying to educate the public on the frequency of cancer and other detrimental conditions, but have we sufficiently taken stock of our efficiency in recognizing the condition after the public has come to us? With the aid of surgery, roentgen rays, and radium we have some idea of what we can do in treatment, although these agents are still in an experimental stage. There is one generalization which may be safely and fairly made, and that is: the earlier the stage of the neoplastic growth, the more readily it responds to treatment, which means that we must attempt to improve our diagnostic methods so that we shall be able to recognize all malignant and potentially malignant conditions early.

I have no means of determining your diagnostic efficiency, but I have had the opportunity of studying the efficiency of a group of well trained, comparatively young men, all graduates of Class A medical schools in this or other countries, and I dare say that their diagnostic ability is equal to, at least, that of the general medical practitioner. I have taken, as part of my material, the results of a comparative study of the preoperative instructions or diagnoses, and the actual pathologic conditions found at operation, checked by a surgical pathologist. In order to make my point clear I shall confine my remarks to one organ, that is, the mammary gland, which is very superficial, easily palpable, easily visible, and one of the most frequent sites of benign and malignant neoplastic conditions. The tabulation presents certain facts, in terms of percentages, which are somewhat startling to those of us who have prided ourselves, blindly, on our diagnostic ability. By way of soothing our offended pride, I might say that these data are a credit

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to our profession, if we are willing to admit that there are physical limitations to the diagnostic capability of our five senses. Our chagrin might be lessened, also, by the fact that when clinicians make a positive diagnosis of a malignant condition they are correct in 94.5 per cent of the cases; and this is the percentage we like to quote; it is, however, not the index of our diagnostic efficiency so far as the patient is concerned.

TYPES OF DIAGNOSES

Number of breasts.....	2100
Percentage of positive preoperative clinical diagnoses.....	78.5
Percentage of doubtful or questioned preoperative clinical diagnoses.....	21.5
Percentage of positive preoperative clinical diagnoses of malignancy correct.....	94.5
Percentage of positive preoperative clinical diagnoses of malignancy incorrect.....	5.5
Percentage of doubtful or questioned preoperative clinical diagnoses of malignancy correct.....	62.8
Percentage of doubtful or questioned preoperative clinical diagnoses of malignancy incorrect.....	37.2
Percentage of positive preoperative clinical diagnoses of benignancy correct.....	88.8
Percentage of positive preoperative clinical diagnoses of benignancy incorrect.....	11.2
Percentage of doubtful or questioned preoperative clinical diagnoses of benignancy correct.....	81.8
Percentage of doubtful or questioned preoperative clinical diagnoses of benignancy incorrect.....	18.2
Percentage of such diagnoses as nodule, tumor, mass, or "no diagnosis".....	17.5
Percentage of such diagnoses as nodule, tumor, mass, etc., malignant.....	17.7
Percentage of all breasts malignant.....	51
Percentage of malignant breasts diagnosed positively by clinician correctly.....	77
Percentage of all breasts benign.....	49
Percentage of benign breasts diagnosed positively by clinician correctly.....	50
Percentage of breasts not diagnosed positively in which suspicion was expressed..	50

The 21.5 per cent of doubtful diagnoses means that, after all known methods of clinical diagnosis have been tried, there still remains 21.5 per cent of the breasts in which an honest clinician is not willing to attempt to fool himself. He is willing, however, to admit this percentage and express himself in one of four ways: by making a diagnosis followed by a question mark; by using indefinite terms such as nodule, growth, or mass; by writing "no diagnosis"; or by suggesting that the specimen be removed for diagnosis. He expresses a suspicion of malignancy in 50 per cent of all his doubtful diagnoses, which leaves the making of the diagnosis to someone else. The fact that 21.5 per cent of his diagnoses are doubtful and that he expresses a suspicion in his doubtful diagnoses suggests that he must expect a diagnosis to be made either by the surgeon, who operates, or by an associated surgical pathologist, or some

general pathologist. Now suppose you are the surgeon and have no surgical pathologist, what are you going to do with the 21.5 per cent and the 50 per cent? This is the question which every surgeon faces. When also facing the fact that only 51 per cent of the breast tumors are malignant and that 94.5 per cent of your malignant diagnoses are correct, what is your scientific criterion for operative procedure? Maybe you will say that in a doubtful case, at or above middle age, it is best to do the radical operation; it is better, you might think, to sacrifice a few benign breasts for the sake of radically treating those with cancer. This is a very old way of reasoning and is one which, undoubtedly, is justifiable if there were no way to avoid it; but there is a way whether you have it or not. You are not to be condemned if you haven't it, but you are to be condemned if you do not attempt to have it. The patients with the doubtful diagnoses and the 5.5 per cent of mistakes can be efficiently taken care of. I have seen more than one surgeon who sought this aid for members of his own family when he did not seek it for his patients. In the whole series of 2100 breasts which were studied, not one was unnecessarily treated too radically and not one failed to receive a radical operation when necessary, and this came about by virtue of the fact that all cases were checked, at operation, by a surgical pathologist.

Now there are certain reasons why all breast cases are not checked:

1. You may not have a pathologist.
2. You may not have tried to have a pathologist.
3. There may not be a pathologist near you.
4. You may think you are a great pathologist, especially a great gross pathologist, in which case you simply incise the tumor, immediately after its removal, and pass judgment.
5. You may not believe in frozen sections.
6. Your practice may not be large enough to allow you to pay a pathologist.
7. You may be depending upon the hospital to supply you with a pathologist.
8. You may have lost faith in pathologists because you have had sad experiences with men who call themselves pathologists, or with the so-called intern pathologist who happens to be sojourning in the hospital for a year or two doing everything in the categories of tissue pathology, bacteriology, serology, clinical microscopy, and sometimes roentgenology. These are all reasons, but they are not all good reasons

why your patient should not receive the same diagnostic efficiency you are apt to give your wife, daughter, or other members of your family. Now what is the solution of this problem which we, as the medical profession, must face and try to solve?

The first reason which has been mentioned is your fault and it is not your fault; pathologists are rare and becoming rarer, I believe, for several reasons: Many pathologists have been attracted to serology, immunology, and bacteriology because they are new sciences and apparently offer greater fields for investigation. The pathologist, being of a rather retiring disposition, has not seen fit to force his wares upon you and demonstrate his value. You have, as practitioners, not morally or financially encouraged young men to stay in pathology; tissue pathology is also a new science and is the victim of much observation, chaotic nomenclature, multiple classifications, and crude methods of studying tissues; the pathologists who are at the top today are necropsy pathologists and know little about fresh tissues. Most of them are teachers and spend too much time in teaching bacteriology, serology, immunology, hygiene, and sanitation to devote enough time to tissues to become authorities in the modern sense.

The second reason may be due to that lethargy which exists among all classes of human beings; it is not characteristic, alone, of the medical profession.

The third reason may be explained as was the first.

The fourth is worthy of a few facts; it is a form of overconfidence which many surgeons, even good surgeons, suffer from. By way of clarification some figures might be stated: In a series of 60,645 general patients, 24,368 (40 per cent) came to operation, and 21 per cent of all patients presented surgical pathologic specimens of which 21 per cent required a microscopic examination before the correct diagnosis could be made, and before scientific therapeutics could be administered. Six and eight-tenths per cent of the specimens removed at operation were removed for diagnostic purposes before further operative procedures were carried out. Perhaps you, as surgeons, are great gross diagnosticians, but, if so, you must account for the 21 per cent of diagnoses which must be made with a microscope. I know of a surgeon who, at the end of the week, examines all of his own specimens; this is very commendable, but if he picks up a mistake he must submit his patient to a second operation, a point in efficiency which might be improved on from the patient's standpoint.

The fifth reason is legitimate if you have clearly and completely endeavored to convince yourself, to the fullest possible extent, that frozen sections are not to be depended on. There are some things about frozen sections which must be put down as essential: Good reliable frozen sections cannot be made from tissues that have been dead much over an hour. In fact, I have seen cells disintegrate in less time; they must not be fixed; they must be cut with a sharp knife;



FIG. 363.



FIG. 364.

FIGS. 363 and 364.—Cancer cells in the mammary gland as they appear in fresh tissues with the oil immersion lens.

and they must be handled in normal saline and mounted in such an isotonic solution as Brun's glucose. When made by this method the cells are more beautiful than any fixed and embedded cells I have ever



FIG. 365.—Cancer cells in the uterus as they appear in fresh tissues with the oil immersion lens.



FIG. 366.—Intra-acinic hyperplastic cells (secondary cytoplasia of MacCarty) as they appear in fresh tissues in the breast.

seen (Figs. 363, 364, 365, and 366). There is just as much difference between studying such cells and fixed cells as there is between studying stuffed bird skins and birds in the trees. It is certain that a knowledge

of fixed tissues will assist one in understanding the unfixed fresh tissues, but the cells are very different. A pathologist who has had all of his training with fixed tissues will undoubtedly have some difficulty with unfixed fresh tissues, just as an ornithologist who has been trained only with stuffed skins will have difficulty with birds in the trees. However valuable both fixed tissues and stuffed skins might be, I feel about the tissues as I would about birds, if I were an ornithologist; I should prefer to obtain knowledge from things as they are in their living state, or as near the living state as possible.

The sixth reason why you might not give your patient the benefit of improved efficiency deserves a suggestion. If your practice is not large enough to afford a pathologist then you might join your forces with one or more surgeons, especially those practising in your hospital, and have a pathologist together.

The seventh reason, your dependence on the hospital for your pathologist, might be considered a legitimate one provided you try to assist and influence your hospital authorities in their attempt to see the value of one. In this day of standardization of hospitals many are endeavoring to obtain good pathologists; the demand is much greater than the supply. Perhaps your hospital has tried; have you suggested that some young man be trained for the position? Have you attempted actually to make such a position attractive, or have you simply thought of it as a fine thing, but have not utilized your ability to execute your thoughts?

The eighth, and last, reason you have a certain amount of justification for, although there is no reason for losing faith in the whole field of pathology or in all pathologists. Pathology, as a science, is very young—not within five hundred years of being as old as surgery. It had its real inception in the middle of the nineteenth century; your profession is as old as human written history. Yours is not yet perfect; you can hardly expect pathology to be perfect. It has grown out of a comparatively recent German rejuvenation of the ancient Greek method of making observations, giving names, and making classifications without much attempt at correlation. As a result, names for pathologic conditions, especially neoplasms, are quite different in different lands and text books. There has been no great principle upon which pathology might be made an exact science. This we hope will be one of the products of the twentieth century. It is possible that it will grow out of seeing cells as they are in the body; and perhaps modern operative

surgery will be the condition which will bring forth a new epoch in the history of our youthful science.

Now that we have seen the reasons why you have not a surgical pathologist and have shown that there is a certain significant percentage of your patients in which he can, and should be, of service to you and to them, I must tell you some of the requisites which you and your pathologist must possess in order to make a combination successful. The man whom you select to become your surgical pathologist must first be young; he must be interested primarily in doing something for your patients; he must have some knowledge of the principles of surgery and surgical technic; he must be interested in studying pathology for the benefit of your patients while you are treating them. He must realize that his work requires speed just as your operative procedures require speed; he must, however, be enough of a man never to sacrifice accuracy for speed; when he does not know he must be willing to say so; if he cannot make a diagnosis he must never guess. He must be present constantly while you are operating and must have access to all your clinical data, the patient, and your experience and judgment. As one well known surgeon has said, "The pathologist is not a clairvoyant; he must have the facts." With these qualifications he can be of great value. If he happens to be endowed with the desire and ability for scientific investigation, his field is unlimited; there are new things to be discovered and methods to be improved in tissue pathology. Chiari, the last of the Rokitansky pupils, said, "Die Pathologie der Gewebe ist in Ihrem Anfang," and this, I have found in my experience, to be true. There is so much to be done that it is staggering to any one who is trying to do it. Your reports of your cases will be more complete and your own interest made greater if you have the proper man as your associate. Since it takes two individuals to make this combination work efficiently and since you, as the surgeon, are a part, there are some things which must be required of you. You must be generous and charitable; you must not only assist, but you must encourage your surgical pathologist. Do not slur at his diagnoses when they differ from yours. If he is incorrect, as doubtless he will be sometimes, remember that you have made mistakes and he knows it just as well as you do, sometimes better than you do. If you find something interesting or unusual while you are operating or perhaps in your reading, always call his attention to it. He may not have time to utilize it then, but if he is the right sort he will store it away in his mind or in

notes for future reference, a reference which might some day reflect great credit upon you, your clinic, and the medical profession.

Now that we have had a clear understanding between us let me tell you just one thing which is new in efficiency in diagnosis which the proper surgical pathologist might well try out. Let us suppose that you are dealing with a pathologic condition in the breast and that you believe the figures which have been presented here relative to your efficiency in clinical diagnosis. If the breast, regardless of the age of the patient, shows the presence of a tumor, associated with dimpling



FIG. 367.—A cyst (aa) in the breast associated with a small extracystic stellate carcinoma (see arrow).

of the skin, fixation and discoloration, and no signs and symptoms of acute inflammation, you may safely make the diagnosis of a malignant condition, but all malignant conditions in the breast do not show all of these signs and many show none of them, a group which is becoming larger as the public and family physicians become educated. Many cases of diffuse chronic mastitis are associated with carcinoma of which there are no local palpable manifestations, and many benign palpable tumors such as fibro-adenomas and cysts are associated with minute carcinomas (Fig. 367) which may easily be overshadowed and missed

by too much attention to the tumor itself, and too little search of the whole specimen during the operation. In doubtful cases I, personally, do not believe it is fair to perform a radical operation, but it is fair, with our present knowledge, to remove a sector (not a section) of the mammary gland-bearing structure for immediate examination. The postoperative studies made by Sistrunk and myself do not reveal anything detrimental to the patient by this procedure even when cancer is present. Such a specimen can be studied carefully for three definite histologic pictures which, whether the general pathologist accepts them or not, have the greatest practical value and are based on tangible biologic facts. Thus, the lining of the ducts and acini of the breast consists normally of two layers of cells (Fig. 368). Sometimes, in chronic mastitis, which is always present in carcinoma in my experi-

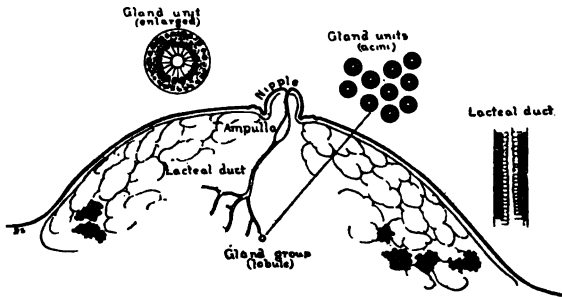


FIG. 368.—A diagram of the breast showing the two types of cells which normally line the ducts and acini.

ence, the inner row of cells is partially or completely destroyed, and is associated with a hyperplasia of the outer row of cells which are morphologically identical with the cells of cancer. Whether or not they are cancer I do not know, but sometimes these same cells are found not only in the acini or ducts but also in the surrounding tissues, a condition which any pathologist would be willing to call cancer. If your pathologist finds the two layers of cells (Fig. 369) he is dealing either with a normal condition or one in which there is a reaction to some disturbing factor. The condition of these cells varies in their relationship to each other so far as size is concerned, but the general presence of the two layers is indicative of a benign condition when seen, and a radical operation is unnecessary. On the other hand, however, if the hyperplastic cells of the outer row have invaded the stroma there is no doubt that a malignant condition is present and that, with our pres-

ent knowledge, a radical operation should be performed. The condition in which the hyperplastic cells have not invaded the stroma (a diagnosis which should be made only after the most thorough and detailed microscopic examination) is one open to question. Should we or should we not perform a radical operation? My experience to date seems to indicate that the removal of the mammary gland-bearing structure is all that is necessary. I have never seen a recurrence after

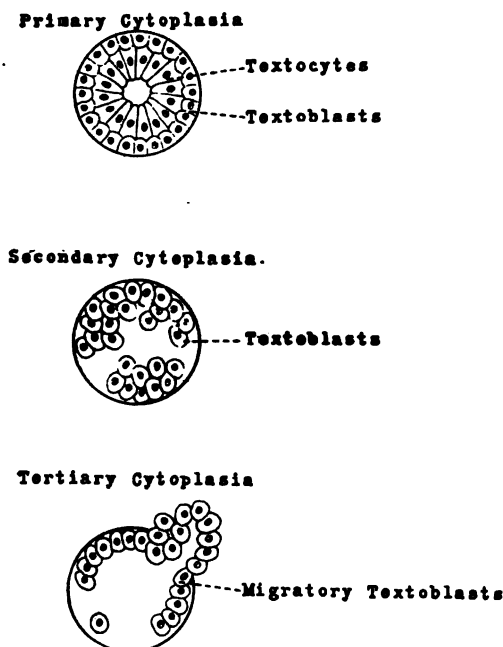


FIG. 369.—Diagram showing the three histologic pictures which are found individually or in combination in chronic mastitis. Primary cytoplasia is a normal condition. Tertiary cytoplasia is malignant. Secondary cytoplasia is a neoplastic condition in which the cells have not invaded the stroma. The cells in secondary cytoplasia are morphologically identical with cancer cells.

such an operation. We have seen, therefore, that there is something new in surgical pathology and that something new has evolved out of the association of a clinical pathologist with the surgeon. It is just such types of service which the surgical pathologist can and should render you and your patients during a single operation. By this means the 5.5 per cent of mistaken diagnoses, the 21.5 per cent of doubtful diagnoses, and the necessary 21 per cent of microscopic diagnoses can be taken care of efficiently without the slightest detriment to your patients.

In conclusion may I state that the medical profession, as a whole, has not reached its greatest efficiency in the diagnosis of neoplasms, but that we have a method by which our efficiency can be and should be increased. All that is lacking to make the diagnostic efficiency greater, in practice, is your encouragement in the making of surgical pathologists with the ideals which have been enumerated. If all surgeons were to spend the next five years trying to follow out the plan presented here we would be able to render a public service of which we might well be proud. If we do not, then we must go along in the same guessing fashion, which I know is not the desire of the majority of the profession. What has been said of the breast is quite as true of the other organs and tissues of the body.

POSSIBLE DEFENSIVE FACTORS IN CANCER OF THE RECTUM: A STUDY OF 102 CASES*

WILLIAM C. MACCARTY AND J. K. W. KEHRER

In June, 1921, one of us (MacCarty) published a series of observations on the "Relation of cellular differentiation and lymphocytic in-

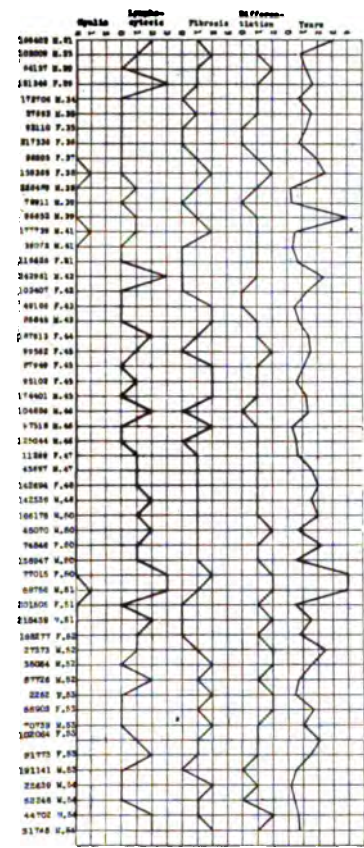


Fig. 370.

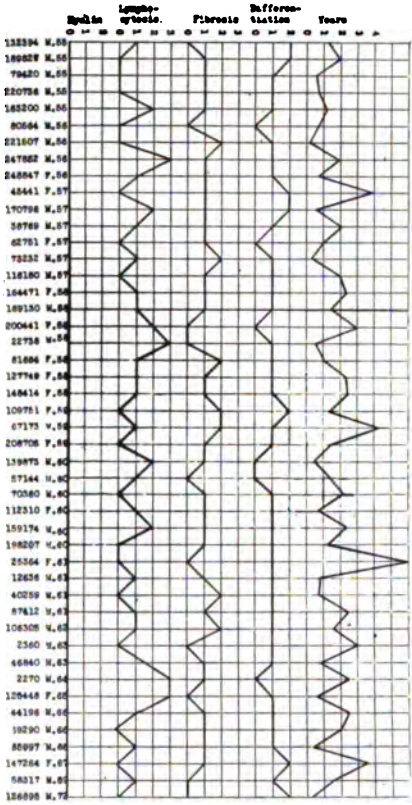


Fig. 371.

filtration to postoperative longevity in gastric carcinoma.”¹ It was then stated that the presence of these factors was associated with an

* Reprinted from the Journal of Laboratory and Clinical Medicine.

82 per cent increase in average length of postoperative life. Since that observation carcinoma of the rectum has been studied in a similar manner, with the exception that such possible factors as fibrosis and

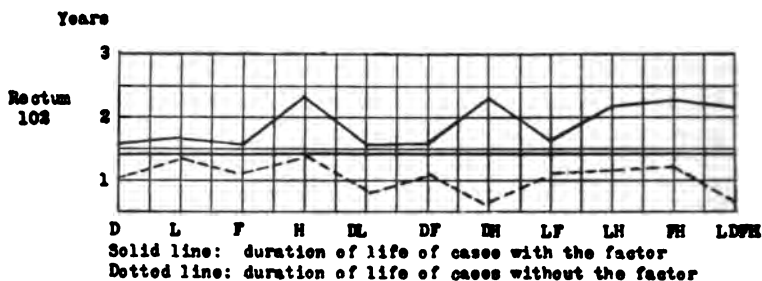


FIG. 372.—Average length of postoperative life with and without factors.

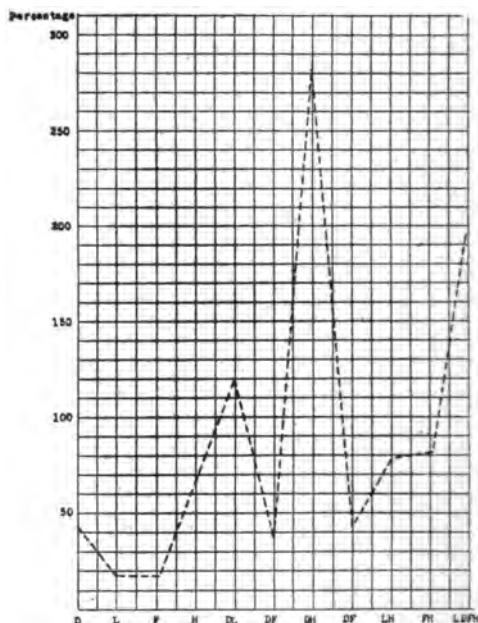


FIG. 373.—Percentage increase of postoperative life with factors checked against postoperative life without factors.

hyalinization were also taken into consideration. In the series 102 cases were studied (Figs. 370 to 373). As in cases of cancer of the stomach, every patient was known to have died of local or distant recurrence following radical resection.

TABULATION OF DATA SHOWN IN FIGURES 370 TO 373

Total number of cases.....	102
Average length of postoperative life (years).....	1.47
	Per cent.
Frequency of differentiation.....	86
Frequency of lymphocytic infiltration.....	57
Frequency of fibrosis.....	75
Frequency of hyalinization.....	2
Frequency of differentiation and lymphocytic infiltration.....	56
Frequency of differentiation and fibrosis.....	70
Frequency of differentiation and hyalinization.....	2
Frequency of lymphocytic infiltration and fibrosis.....	47
Frequency of lymphocytic infiltration and hyalinization.....	1
Frequency of fibrosis and hyalinization.....	2
	Years.
Average length of postoperative life with differentiation.....	1.54
Average length of postoperative life without differentiation.....	1.08
Average length of postoperative life with lymphocytic infiltration.....	1.57
Average length of postoperative life without lymphocytic infiltration.....	1.31
Average length of postoperative life with fibrosis.....	1.53
Average length of postoperative life without fibrosis.....	1.29
Average length of postoperative life with hyalinization.....	2.33
Average length of postoperative life without hyalinization.....	1.44
Average length of postoperative life with differentiation and lymphocytic infiltration.....	1.59
Average length of postoperative life without differentiation and lymphocytic infiltration.....	0.71
Average length of postoperative life with differentiation and fibrosis.....	1.58
Average length of postoperative life without differentiation and fibrosis.....	1.15
Average length of postoperative life with differentiation and hyalinization.....	2.33
Average length of postoperative life without differentiation and hyalinization.....	0.61
Average length of postoperative life with lymphocytic infiltration and fibrosis.....	1.65
Average length of postoperative life without lymphocytic infiltration and fibrosis.....	1.17
Average length of postoperative life with lymphocytic infiltration and hyalinization.....	2.25
Average length of postoperative life without lymphocytic infiltration and hyalinization.....	1.27
Average length of postoperative life with fibrosis and hyalinization.....	2.33
Average length of postoperative life without fibrosis and hyalinization.....	1.28
Average length of postoperative life with lymphocytic infiltration, differentiation, fibrosis, and hyalinization.....	2.25
Average length of postoperative life without lymphocytic infiltration, differentiation, fibrosis, and hyalinization.....	0.76

From these data certain legitimate generalizations may be made:

1. The average length of postoperative life, when the factors, lymphocytic infiltration, fibrosis, hyalinization, and differentiation, are present, is greater than when the factors are absent.
2. The average length of postoperative life, when some of the factors are present, is 40 per cent greater than the average length of

life for the 102 patients, and 146 per cent greater than when none of the factors is present.

3. With all four factors present in combination the average length of postoperative life is 196 per cent greater than if none of the factors is present.

In conclusion it may be stated that from this series of observations, lymphocytic infiltration, cellular differentiation, fibrosis, and hyalinization seem to play a part in prolonging the postoperative length of life.

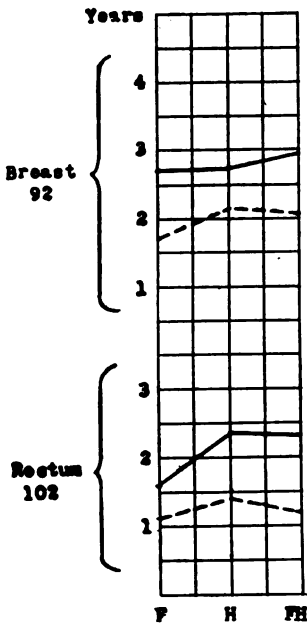
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THE RELATION OF FIBROSIS AND HYALINIZA- TION TO LONGEVITY IN CANCER: A STUDY OF 194 CASES*

WILLIAM C. MacCARTY

In June, 1921, I published a series of observations on the relation of local lymphocytic infiltration and cellular differentiation to the



Solid line: duration of life of cases with the factor
Dotted line: duration of life of cases without the factor

Fig. 374.—Average length of postoperative life with and without factors.

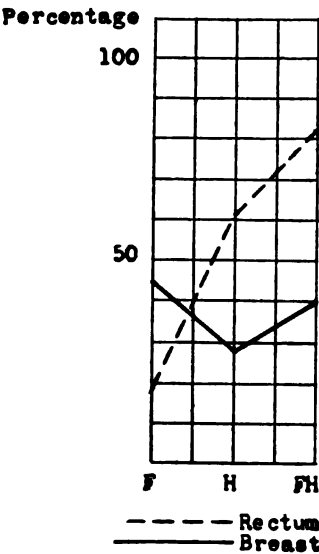


Fig. 375.—Percentage increase of postoperative life with factors checked against postoperative life without factors.

length of postoperative life in gastric carcinoma.¹ While making those observations no special attention was paid to the relation of fibrosis

* Presented before the American Association of Bacteriologists and Pathologists, Cleveland, Ohio, March 26, 1921. Reprinted from the Journal of Laboratory and Clinical Medicine.

and hyalinization to postoperative life. It was not done because both fibrosis and hyalinization are rather infrequent in the series of gastric carcinomas which has come under my observation. There are, however, two organs in which these factors (Figs. 374 and 375) are more frequent, and it was thought that a study of these might throw some light on the problem of the defensive mechanism in cancer. Two series of patients, all of whom had died of recurrence or metastasis following radical resection, were studied.

OBSERVATIONS IN 194 CASES

	Breast.	Rectum.
Cases	92	102
Average length of postoperative life.....	2.5 years	1.47 years
Frequency of associated fibrosis	68 per cent	75 per cent
Frequency of associated hyalinization.....	52 per cent	2 per cent
Frequency of associated fibrosis and hyalinization.....	52 per cent	2 per cent
Average length of postoperative life with associated fibrosis.....	2.72 years	1.53 years
Average length of postoperative life without associated fibrosis.....	1.87 years	1.29 years
Average length of postoperative life with associated hyalinization.....	2.81 years	2.33 years
Average length of postoperative life without associated hyalinization.....	2.21 years	1.44 years
Average length of postoperative life with associated fibrosis and hyalinization.....	2.89 years	2.33 years
Average length of postoperative life without associated fibrosis and hyalinization.....	2.05 years	1.28 years

The following generalizations may be made:

1. The frequency of fibrosis in association with cancer of the breast and rectum is practically the same in both organs.
2. The frequency of hyalinization in association with cancer of the breast is greater than in cancer of the rectum.
3. When fibrosis is present in association with cancer of the breast and rectum the postoperative length of life is increased 34 per cent.
4. When hyalinization is present in association with cancer of the

breast and rectum the postoperative length of life is increased 40 per cent.

5. When the two factors, fibrosis and hyalinization, are present in combination in association with cancer of the breast and rectum the postoperative length of life is increased over 56 per cent.

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'21-74

FACTORS WHICH INFLUENCE LONGEVITY IN CANCER: A STUDY OF 293 CASES*

WILLIAM C. MACCARTY

Practically every surgeon, clinician, and pathologist who follows postoperative results in cancer has occasionally been surprised to find that in some of his extensive cases patients live much longer postoperatively than others with easily removable small growths. Such experience with cancer, after resection, led to the following investigation:

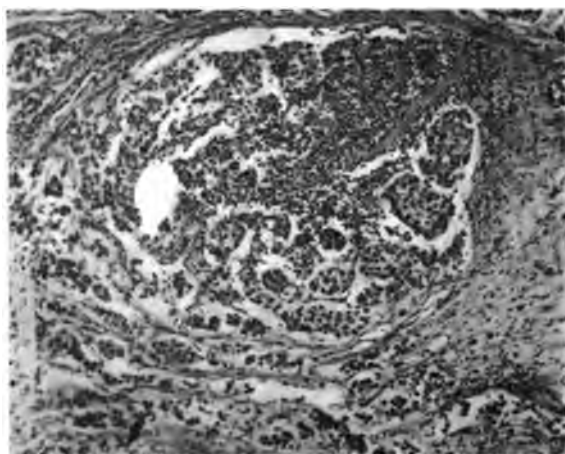


FIG. 376.—Lymphocytic infiltration intimately associated with cancer cells.

The material for study consisted of ninety-nine cancers of the stomach,¹ ninety-two cancers of the breast, and 102 cancers of the rectum. All the patients were known to have died of recurrence or metastasis after extensive radical removal of the growth. The specimens were studied to determine the frequency and possible influence of lymphocytic infiltration, fibrosis, hyalinization, and cellular differentiation on postoperative longevity. Lymphocytic infiltration, fibrosis, and

* Presented before the Minnesota Pathological Society, Minneapolis, November 15, 1921. Reprinted from the *Annals of Surgery*.

hyalinization were considered to be present only when they were found in intimate association with the cancer cells (Figs. 376, 377, and 378). By cellular differentiation is meant the structural changes which take place in the evolution of an adult tissue cell (Fig. 379).

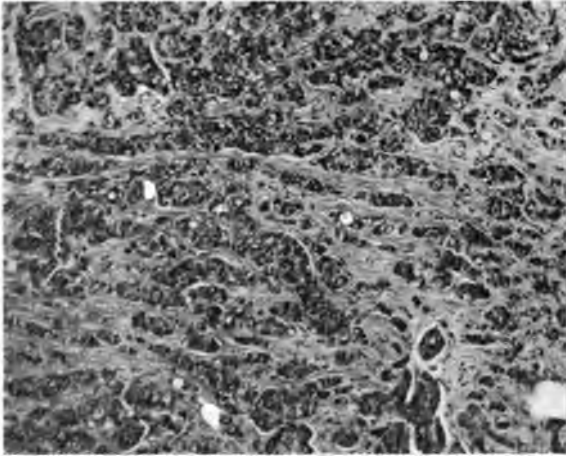


FIG. 377.—Fibrosis intimately associated with cancer cells.

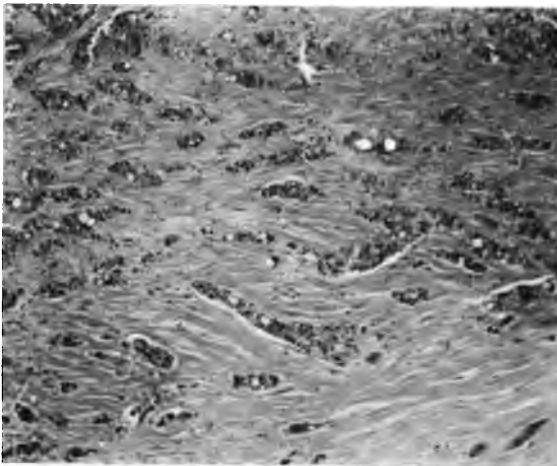


FIG. 378.—Hyalinization intimately associated with cancer cells.

An examination of the facts charted in Figure 380 reveals that the average length of postoperative life is greater when the factors are present singly or in combination. When the facts are studied from the

standpoint of percentage increase of postoperative length of life and checked against the average postoperative length of life with the presence of the factors, it may be seen (Fig. 381) that in the whole series there is a marked increase. If one charts the facts, from the standpoint of percentage increase in postoperative life in the presence of one factor (alone or in combination), checked against the absence of that factor it may be seen (Fig. 382) that differentiation and hyalinization

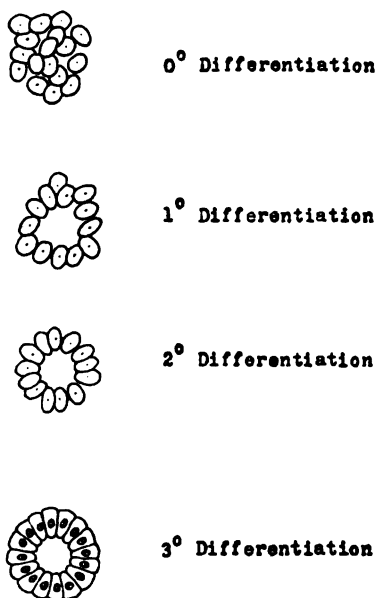


FIG. 379.—Degrees of cellular differentiation based on the stages of differentiation of specific tissues during embryologic development. In the stage without differentiation the cells are merely arranged in masses. In the first degree of differentiation the cells assume the general alignment of the adult tissue, but without arrangement of the axes of the cells as in the adult tissue cells. In the second degree of differentiation the axes are parallel or form radii of a sphere or circles. In the third degree the cells assume the adult morphology of the units of the specific tissue.

apparently play the greatest rôle in influencing the longevity. This is more striking if the percentage difference between the average length of postoperative life with and without the factors (alone and in combination) is checked against their absence (Fig. 383).

In conclusion it might be stated that the uniform consistency of increased length of postoperative life in the presence of lymphocytic infiltration, fibrosis, hyalinization, and cellular differentiation suggests

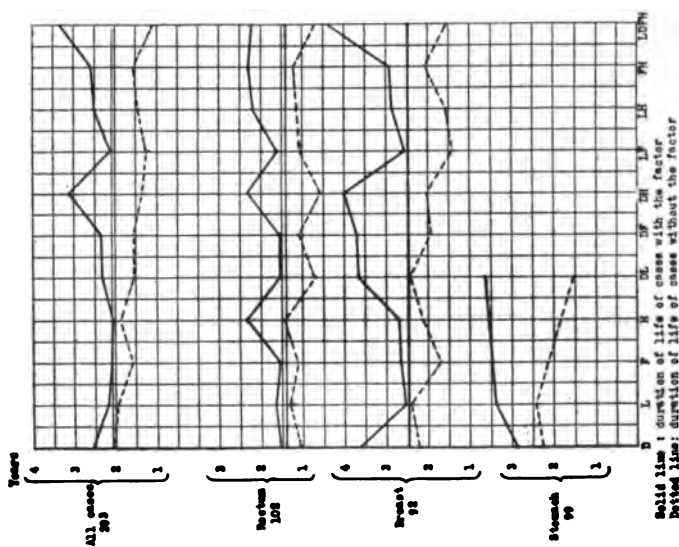


FIG. 380.—Average length of postoperative life with and without factors.

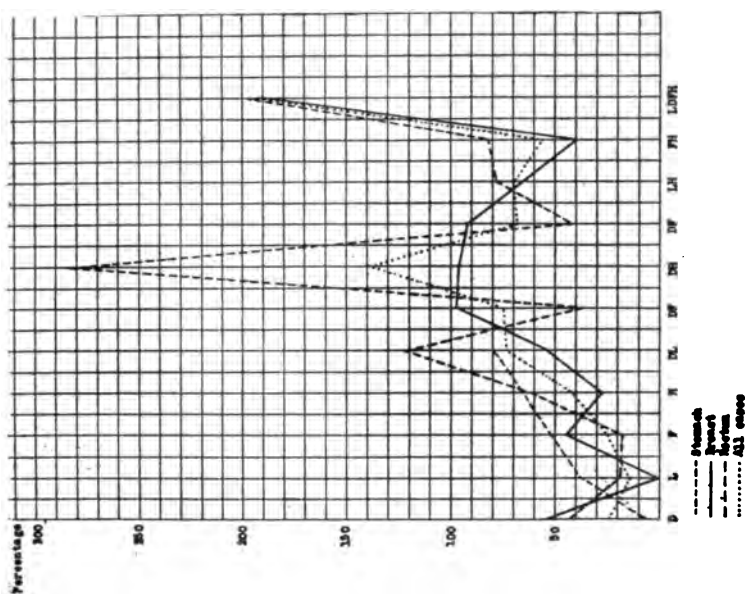


FIG. 381.—Percentage increase of postoperative life with factors checked against postoperative life without factors.

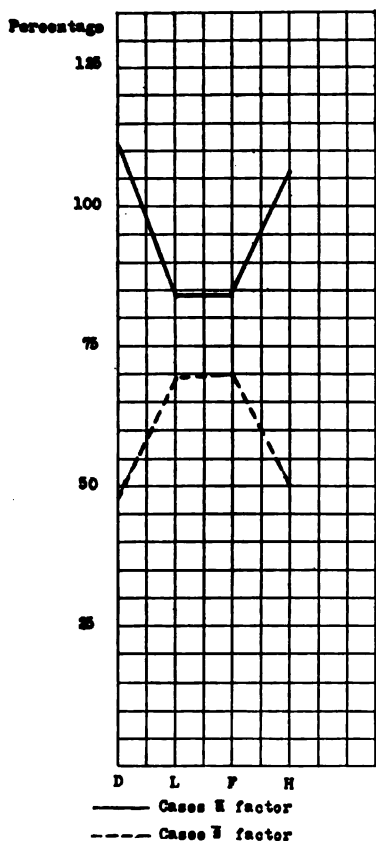


FIG. 382.—Average percentage increase of postoperative life in the presence of one factor (alone and in combination) checked against the absence of the factor.

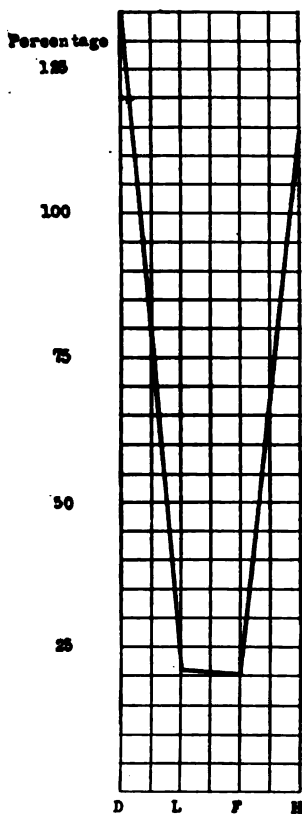


FIG. 383.—The percentage difference between the average length of postoperative life with and without the factors (alone and in combination) checked against the absence.

that these factors play a significant rôle, as a part of the natural defensive mechanism against cancer after it has once developed.

DATA OBSERVED IN THE SERIES OF 293 CASES

	Stomach.	Breast.	Rectum.	Total.
Cases	99	92	102	293
Average length of postoperative life	2.62 years	2.5 years	1.47 years	2.19 years
Frequency of differentiation	65 per cent	8.6 per cent	86 per cent	53.2 per cent
Frequency of lymphocytic infiltration	91 per cent	60 per cent	57 per cent	69 per cent
Frequency of fibrosis		68 per cent	75 per cent	71 per cent
Frequency of hyalinization		52 per cent	2 per cent	27 per cent
Frequency of differentiation and lymphocytic infiltration		6 per cent	56 per cent	31 per cent
Frequency of differentiation and fibrosis		7 per cent	70 per cent	38 per cent
Frequency of differentiation and hyalinization		4 per cent	2 per cent	3 per cent
Frequency of lymphocytic infiltration and fibrosis		40 per cent	47 per cent	43 per cent
Frequency of lymphocytic infiltration and hyalinization		27 per cent	1 per cent	14 per cent
Frequency of fibrosis and hyalinization		52 per cent	2 per cent	27 per cent

	Years.	Years.	Years.	Years.
Average length of postoperative life with differentiation	2.73	3.65	1.54	2.64
Average length of postoperative life without differentiation	2.56	2.37	1.08	2.0
Average length of postoperative life with lymphocytic infiltration	2.73	2.51	1.57	2.6
Average length of postoperative life without lymphocytic infiltration	2.7	2.48	1.31	2.16
Average length of postoperative life with fibrosis		2.72	1.53	2.12
Average length of postoperative life without fibrosis		1.87	1.29	1.58
Average length of postoperative life with hyalinization		2.81	2.33	2.57
Average length of postoperative life without hyalinization		2.21	1.44	1.82

DATA OBSERVED IN THE SERIES OF 293 CASES—*Continued*

	Years.	Years.	Years.	Years.
Average length of postoperative life with differentiation and lymphocytic infiltration.....	2.8	3.78	1.59	2.72
Average length of postoperative life without differentiation and lymphocytic infiltration.....	1.55	2.45	0.71	1.57
Average length of postoperative life with differentiation and fibrosis.....		3.87	1.58	2.72
Average length of postoperative life without differentiation and fibrosis.....		1.96	1.15	1.55
Average length of postoperative life with differentiation and hyalinization.....		4.0	2.33	3.16
Average length of postoperative life without differentiation and hyalinization.....		2.04	0.61	1.32
Average length of postoperative life with lymphocytic infiltration and fibrosis.....		2.69	1.65	2.17
Average length of postoperative life without lymphocytic infiltration and fibrosis.....		1.4	1.17	1.28
Average length of postoperative life with lymphocytic infiltration and hyalinization.....		2.76	2.25	2.56
Average length of postoperative life without lymphocytic infiltration and hyalinization.....		1.63	1.27	1.47
Average length of postoperative life with fibrosis and hyalinization.....		2.89	2.33	2.61
Average length of postoperative life without fibrosis and hyalinization.....		2.05 †	1.28	1.66
Average length of postoperative life with lymphocytic infiltration, differentiation, fibrosis, and hyalinization.....		4.4	2.25	3.32
Average length of postoperative life without lymphocytic infiltration, differentiation, fibrosis, and hyalinization.....		1.52	0.76	1.14

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THE DIABETIC PATIENT AS A SURGICAL RISK*

DAVID M. BERKMAN

The material for this paper is drawn largely from a study of the subject, the results of which I have published. I have now added to the statistics data collected recently, and I shall attempt to bring out more particularly the question of anesthesia in its relation to the surgical mortality in diabetic patients.

The first important point to be considered in any proposed surgical procedure is the choice of an anesthetic which will permit the operator to bring his work to a successful technical conclusion. It must be borne in mind that it is rarely possible to estimate beforehand the procedure which will be followed in an abdominal operation. While many skilled surgeons perform certain types of laparotomies successfully under a local anesthetic, the greater number are handicapped in working on abdominal viscera by not having the patient under a general anesthetic.

It is difficult to classify the surgical conditions that are to be found in diabetic patients, since such classification may be approached from various angles. Falta divides his patients into two groups, those in whom the surgical conditions will tend to or already do bear a relationship to diabetes, and those in whom there is no such relationship. Falta's description of the first group carries no implication relative to the cause of diabetes, but catalogs these surgical diseases as potential influences on diabetes. I should include in this group all infectious conditions, including furuncle, carbuncle, and gangrene mentioned by him, and all definite affections of the gallbladder, bile passages or pancreas, and diseases of the thyroid. Our general impression is that following successful operation for the foregoing conditions the tendency is toward improvement of the diabetes.

I would make two groups of the surgical conditions of diabetic patients, the vital, comprised of conditions threatening the life or fundamental health of the patient immediately or ultimately, and the

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nonvital. There is also the sharp distinction between the emergency and the nonemergency operation. The so-called acute abdomen permits no delay, and in acute infections, even in nonvital locations, delay may prove dangerous, since the infection often disturbs metabolism to the extent that preoperative dietary measures are unavailing. Our observations have shown that in the presence of diabetes the mortality in operations for septic conditions is twice that found in nonseptic conditions. Nephritis, arteriosclerosis, old age, obesity, and so forth, will contribute to the surgical hazard in proportion to the degree of involvement. To these may be added cardiac and circulatory diseases, debilitation from any cause, and the surgical procedure itself aside from any complication.

The increasing excellence of the methods of administering anesthetics and better methods of preoperative treatment have brought the surgical mortality of diabetic patients within a reasonable limit. I shall not describe here the medical preparation of diabetic patients for surgery. In general, the purpose is to render the urine free from sugar, to detect any tendency to acidosis, and to bring the alkaline reserve to a point where surgical intervention may be attempted with reasonable safety. The physician's preoperative observation of patients enables him to withhold from surgery the occasional patient who is so close to the borderline of dangerous acidosis as to make operative procedure prohibitive. It is by the careful selection of cases that surgical mortality of diabetic patients is kept relatively low.

In our cases acidosis followed by death in coma has played a very small part in the mortality. The deaths have been due largely to the usual postoperative sequelæ and the accidents commonly encountered in a general surgical service, such as the development of pneumonia, peritonitis, and embolism. Infection of one type or another seems to be a predominating factor. Whether the diabetes predisposes to infection or whether the diabetic patient succumbs to infection more readily than the nondiabetic is difficult to determine; both factors probably play a part.

I have revised my previous statistics to include seventy-four operations performed in the Mayo Clinic on sixty-seven patients within the past two years, making a total of 233 separate operations performed on 201 patients. The mortality, based on the number of operations, is 6.4 per cent; based on the number of patients, it is 7.4 per cent. Of the fifteen patients who died, only three died in coma: one after the use

of ether, one after local infiltration with novocain, and one after spinal anesthesia. Ether was used 140 times in the entire series of cases; nine deaths occurred in this group, a mortality of 6.4 per cent. Local injections of novocain or cocain were used eighty times, followed by three deaths, a mortality of 3.7 per cent. Nitrous oxid was used eight times, followed by death in one instance. Spinal anesthesia was employed on two patients, one of whom died in coma. Three patients were operated on without an anesthetic; morphin and scopolamin were given before operation. One of these patients died a number of days later of a postoperative complication. Nitrous oxid has not been used in the Clinic extensively until the last two years, but it is being found a very useful type of general anesthetic in certain short operations, such as amputation. My own observation of the use of spinal anesthesia does not convince me that it has any great advantages over ether, nitrous oxid, or local infiltration used under their proper indications. Spinal anesthesia involves a specialized, rather delicate technic, not unattended with the risk of accident, although when expertly administered it undoubtedly is a spectacular exhibition. I cannot say that I favor its use on the diabetic patient. Novocain, either by the infiltration or the nerve block method, is certainly the anesthetic of choice whenever it is adequate for the procedure contemplated. The use of ether in diabetic patients has received considerable censure for years. The experience of the anesthetist, the degree and time of the anesthesia, and the workmanship of the operator play vital parts in the success or failure of this anesthetic. We give ether by the so-called open method; thus the degree of anesthesia is very light, which is particularly important in diabetic patients. Combined anesthesia often is employed by the local injection of novocain in conjunction with ether; the very lightest degree of anesthesia is often sufficient. Occasionally the operation may be begun under nitrous oxid and oxygen, and ether substituted in the later stages. Ether has been given to the greater number of our diabetic patients requiring operation with a mortality rate which, I believe, justifies the choice. It is argued that beyond the immediate risk of operation there is the danger of increasing the degree of diabetes by the use of ether. I have not had a great many opportunities to observe the postoperative effect of ether over a prolonged length of time, but so far as I have been able to determine the diabetes has not increased, or at least an increase has not been apparent in the first few weeks of postoperative convalescence.

One factor has had a distinct bearing on our mortality statistics; we have performed practically no emergency operations on patients with severe diabetes. On the other hand, a large proportion of the patients have had major operations for serious conditions. I have tabulated briefly the salient facts concerning the patients who died. Death occurred in twelve instances as the direct result of varied postoperative complications rather difficult to associate directly with the diabetic condition. Mainly the deaths were following major operations on patients with poor general health, a condition which would increase the surgical hazard without the presence of diabetes.

An analysis of the fifteen deaths recalls the two important causes of death following operation on diabetic patients, namely, postoperative infection and postoperative acidosis. By the careful selection and management of patients the latter may be obviated to a large extent. Only 1.3 per cent of the operations in this series were followed by acidosis and coma. A careful study of the blood sugar concentration and the carbon dioxid combining power of the plasma give the best indication of the tendency of the patient toward acidosis. Postoperative infection, then, becomes our greatest danger. This factor is so intimately associated with surgical skill, judgment, and postoperative care that I venture to repeat Joslin's statement that the most trifling surgical procedure on the diabetic patient is deserving of the highest available surgical skill (Tabulation).

In conclusion, I would state that the physician, assisted by the high degree of proficiency which has been attained in methods of anesthesia throughout the country, may, under proper conditions, bring surgical relief to a large number of patients who have a complicating diabetes. A reasonable mortality rate may be confidently anticipated, but only under the most painstaking cooperation between internist, anesthetist, and surgeon.

TABULATION OF DIABETIC DEATHS IN THE HOSPITAL

Case.	Sex, age.	Operation.	Cause of death.	Anes- thetic.	Days after operation.	Sepsis.
A160174	M. 29	Tonsillectomy.	Diabetic coma.	Local.	Two.	+
A176239	F. 55	Thyroidectomy.	Bronchopneumonia.	Ether.	Three.	0
A196666	M. 20	Thyroidectomy.	Bronchopneumonia and myocarditis.	Ether.	Two.	0
A204158	M. 46	One-stage Kraake for carci- noma of the rectum.	Diabetic coma.	Ether.	Four.	0
A226214	M. 57	Suprapubic cystostomy.	Pyelonephritis.	Local.	Fifty-two.	+
A256509	M. 62	Permanent colostomy and posterior excision of rectum and anus for cancer of the rectum.	Gas bacillus septic- mia.	Ether.	Twenty- eight.	0
A268038	M. 39	Umbilical herniotomy.	Bilateral pulmonary fat embolism.	Ether.	Six.	0
A268094	F. 58	Thyroidectomy.	Bronchopneumonia.	Ether.	Five.	0
A311026	F. 70	Vaginal hysterectomy.	Pelvic peritonitis.	Ether.	Eleven.	0
A310651	M. 37	Thyroidectomy.	Bronchopneumonia.	Local.	Four.	0
A323698	F. 66	Subtotal abdominal hyster- ectomy. Two weeks later enterostomy for obstruction.	Intestinal obstruction.	Ether local.	Fourteen	0
A335684	F. 38	Thyroidectomy.	Bronchopneumonia.	Local.	Three.	0
A341196	F. 48	Subtotal abdominal hyster- ectomy.	Cysto-ureteropyelo- nephritis.	Ether.	Three.	0
A359970	M. 59	Amputation of leg.	Diabetic coma.	Spinal.	One.	+
A371517	F. 45	Cholecystectomy and chole- dochoostomy.	Hepatic degeneration.	Local and ether.	One.	0

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SURGICAL ANESTHESIA IN RELATION TO DIABETES MELLITUS*

REGINALD FITZ

A successful surgical operation on a diabetic patient depends largely on three factors, the preoperative preparation of the patient, the skill of the surgeon, and the method of anesthesia. Four types of anesthesia can be safely used, intraspinal or paravertebral, nitrous oxid or nitrous oxid and oxygen, local with cocain or novocain, and ether. In discussing any anesthetic in relation to diabetes, however, it should be remembered that all patients with this disease are abnormally poor surgical risks for two reasons, first, the danger of postoperative infection, and second, the danger of postoperative acidosis. Foster has laid down a general rule in regard to the surgical treatment of diabetes which is worth emphasizing. Patients with hyperglycemia of more than 0.35 per cent or a carbon dioxid combining power of the blood plasma of less than 40 volumes per cent cannot be expected to survive any operative procedure. Patients with hyperglycemia above this amount and without acidosis often die of postoperative infection. Patients without hyperglycemia, but with more than this amount of acidosis, are inclined to pass into coma.

Intraspinal or paravertebral anesthesia has been used in but few reported cases of diabetes. Joslin has found it satisfactory in several of his instances, although he believes that it is often undesirable because of the nervous tension to which it subjects the patient. I have observed one patient with a mild diabetes who was operated on for hernia under intraspinal anesthesia and who subsequently developed an acidosis severe enough to threaten life. On this account, chiefly, I am prejudiced against this type of anesthesia, the more so because no careful data have been recorded with regard to the pharmacologic effect of such a method of anesthesia in a large series of diabetic cases.

Nitrous oxid or nitrous oxid and oxygen are frequently employed for anesthesia in diabetes, especially for minor operations. Both of

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these anesthetics seem harmless. Nausea or vomiting rarely follows, which is an important point in their favor, as the prognosis for a nauseated diabetic patient is far worse than for one with a sound stomach capable of absorbing fluids. There is one serious objection to these anesthetics for major operations, namely, difficulty in administration. One often sees an operation begun under gas-oxygen anesthesia and finished under ether. It may be possible in this fashion to minimize the amount of ether given, which is important. On the other hand, it is sometimes difficult to adjust the ether-oxygen mixture so perfectly that the patient does not become cyanosed, or restless. These complications should be carefully avoided on account of the production of increased hyperglycemia.

I have studied the effect of gas-oxygen anesthesia on the blood chemistry of several diabetic patients and have been impressed with the reaction which it apparently produces. It causes hyperglycemia without acidosis, and even seems to reduce a moderate acetonemia. On this account, theoretically, it is an excellent anesthesia for diabetics. This opinion is supported by Joslin's practical experiences. He considers nitrous oxid or gas-oxygen the best general anesthetic for diabetics provided they are administered by one trained in their use.

Local anesthesia with cocain or novocain, or general anesthesia with ether, will probably continue to be the two anesthetics most widely used. Patients with diabetes complicated by infection and marked acidosis, who appear to be poor surgical risks on this account, often survive minor operations under local anesthesia and improve surprisingly when the infection is properly treated.

Local anesthesia, too, is the anesthetic of choice in operations such as tonsillectomy or the removal of teeth. On the other hand, it may have a serious disadvantage for major operations. If a wide area of skin is infiltrated to procure anesthesia, the area along the line of incision may become infected and be followed by chronic suppuration resulting in lowered carbohydrate tolerance. On the whole, local anesthesia is satisfactory in most cases; it is not often followed by acidosis or infection.

Ether is the most popular anesthetic from a surgeon's point of view. It has certain theoretic objections in cases of diabetes, as it is known to cause acidosis and hyperglycemia in the normal person; this reaction may be exaggerated in patients with diabetes. Because of this most internists advise against its use, preferring gas-oxygen or novocain.

Berkman, of the Mayo Clinic, is the chief advocate for the general use of ether in operating on diabetic patients, believing that it is the anesthetic of choice when given under proper conditions. If ether is employed both anesthetist and surgeon must remember Crile's statement: "The surgeon and anesthetist alike must realize that during an operation each is draining the store of reserve alkalinity. The surgeon must use gentle manipulation and produce the least possible trauma in order to conserve the patient. The anesthetist must use the lightest possible even anesthesia administered with the least psychic trauma."

Experience with ether in cases of diabetes in the Mayo Clinic during the last year bears out Berkman's earlier views. The amount of ether given to each patient, however, was small and the duration of anesthesia was short. In order to demonstrate this fact graphically one hundred records of patients who received ether anesthesia for abdominal operations were analyzed as follows:

The weight of each patient, the volume of ether administered, and the duration of anesthesia from the moment the drug was first inhaled until it was stopped were recorded. These results were averaged and tabulated. Similar data from the surgical records of a representative general hospital were obtained and averaged for comparison. In each series the operations were performed on chronic nondiabetic patients without evidence of acute infection, and, in order to rule out any question of personal selection, were selected indiscriminately from the mass of material at hand. The results of this study are tabulated:

TABLE
100 ABDOMINAL OPERATIONS

	Mayo Clinic group:	Control group:
Average weight of patients.....	64.5 kg.	61.3 kg.
Average volume of ether for each patient.....	170 c.c.	267 c.c.
Average duration of anesthesia for each patient.....	48 minutes	102 minutes

As may be seen, the patients in the Mayo Clinic series inhaled ether in less amount, on the average, and for a much shorter time than did the control patients. This is of the utmost importance in operations on diabetic patients and is probably one of the factors accountable for the low mortality reported by Berkman, especially since the diabetic patients in the Mayo Clinic are etherized with special circumspection and would presumably show even lower per-

centage than those recorded. In order to minimize the amount of ether given a combination of local and ether anesthesia can be satisfactorily used. For example, Dr. W. J. Mayo recently performed a hysterectomy on a diabetic patient under such combined anesthesia. The patient had developed marked acidosis during preliminary treatment. She inhaled only 120 c.c. of ether, had a perfect anesthesia, and subsequently made an uneventful recovery.

A certain percentage of diabetics will do badly, necessarily, despite the most careful preoperative care, the best surgery, and the most skillfully administered anesthetic. These patients are not always those with the severest type of the disease nor those who are given any particular type of anesthetic. In operating, therefore, the surgeon and the anesthetist must comprehend the severity of the condition and be on guard for unusual manifestations.

On the whole, certain general rules with regard to the anesthesia of diabetic patients can be formulated. All diabetic patients are abnormally poor surgical risks and must be recognized as such by the internists, surgeons, and anesthetists. The preoperative and post-operative care of the patient, the type of anesthetic used, and the skill with which it is given are of as much importance in prognosis as is the technic of the operation.

A patient who has a blood sugar concentration of more than 0.85 per cent or a carbon dioxid combining power of the plasma of less than 40 volumes per cent is an extremely hazardous surgical risk for any operation under any anesthesia.

Spinal anesthesia may be dangerous for routine use in diabetes and unless there is some direct indication for its employment should not be used.

Nitrous oxid or nitrous oxid and oxygen are safe inhalation anesthetics provided the technic of their administration is perfect. Cyanosis or struggling should be avoided.

Local anesthesia with cocain or novocain is the safest anesthesia for general use in diabetic patients.

Ether anesthesia is well borne in many cases. It should not be given in septic cases, however, and must never be given unless the operation can be performed rapidly and unless a small amount of the drug can be employed. If it has to be used in a doubtful case it can be satisfactorily combined with local anesthesia so that the amount of anesthetic inhaled is minimized.

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LATEST ACHIEVEMENTS OF THE ART OF LOCAL, REGIONAL, AND SPINAL ANESTHESIA*

GASTON L. LABAT

In unfolding the literature on local and regional anesthesia, one is impressed by the slow but steady progress with which these methods have found their way into general surgery. Although they have not been universally adopted as a routine procedure, in many clinics on the continent they have given a mortal blow to inhalation narcosis during the past few years.

Since the days of the innovation of local and regional anesthesia by Reclus, Schleich, Selheim, Corning and Bier, every effort has been strained to improve the results already obtained. Cocain, which was the only local anesthetic of that time, fell almost completely into disuse when stovain and novocain came to light the same year. These drugs, particularly the latter, gave a new impetus to the methods on which cocain had already cast a heavy shadow.

After passing from the simple intradermal infiltration to the injection of the deeper structures along the line of incision, it could not be expected that local anesthesia would give any better results than those already obtained by the pioneers, for the simply obvious reason that infiltration along the line of incision would always prove satisfactory when applied to interventions of the very minor types, or when the structures under the direct influence of the cutting instruments could be the site of repeated injections during almost the entire stage of the operative procedure. "The circular anesthesia" of Hackenbruch was a real progress. It stands midway between local and regional anesthesia, in that the anesthetic fluid is distributed around the operative field.

It does not seem that local anesthesia gradually developed into regional anesthesia which is based on entirely different principles, but the constant desire for widening the scope of operations capable of being performed without the aid of general anesthesia suggested the new procedures of nerve blocking by paravertebral and intraspinal injections.

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The last decade was very prosperous in many an interesting feature of development. The important contributions of Braun, L  wen, Finsterer, Kappis, Kullenkamp, H  rtel, Matas, Crile, Harris, Allen, Pauchet, Sourdat, and a host of others have converted the method into an art and laid its fundamentals on a scientific basis. It is with the refinement of this art that we are chiefly concerned in this paper.

Taking for granted that a thorough knowledge of nerve distribution is required of the surgeon who wishes to, I shall not say succeed in, but attempt nerve blocking, the technic itself exhibits such characteristic features pertaining to a specialty that he finds himself completely hopeless without a fair knowledge also of the principles of the method itself. He has perhaps read hundreds of articles in which indications are set forth, advantages established, and cases reported. He has perhaps watched many operations performed under regional or spinal anesthesia and has left the operating room greatly impressed with the tremendous work that can be accomplished with a few injections of novocain. Some inquire of the strength and the quantity of solution used, and so forth. But, I am sorry to say, there are very few articles from which the ordinary physician is able to gather the true elements of the art of inducing a good regional or spinal anesthesia. Most of the literature conveys an impression of anxiety to arouse the enthusiasm of the reader by telling him how much can be done with the method and how safe it is, or, conversely, to discourage by pointing out its dangers and reporting after-effects or fatalities. Whatever be the subject under consideration, one should first study the principles of a method and all the circumstances attending its practice before making any attempt to use it. The presence of some anesthetic fluid in a human body is not always followed by anesthesia; but its presence in the correct place will never fail to produce the desired result. Let us, therefore, learn how and where to inject it. If some patients are said to be "bad subjects for local," let us study the ways and means of bettering their condition by finding what is wrong with them and by trying to correct it. If the injection is followed by pain or sloughing or produces toxic symptoms, let us see what is the matter with it, carefully observing the symptoms so that we may be able to attribute them either to the anesthetic fluid or to the adrenalin added to it. We must also beware of the coincidence of some other symptom due to a sudden attack of the disease. Patients suffering from cholecystitis with stones have sometimes exhibited an attack shortly after the injection of morphin, but preceding the anesthesia.

It might have happened during the anesthetic procedure and might then have been interpreted by the inexperienced as a result of the anesthetic drug. Let us study briefly the chemistry, pharmacology, and physiologic effects of the drugs we propose to inject and learn the ways and means of combating their occasional after effects. In studying carefully the clinical aspect of our patients we shall learn how to distinguish between an after effect and a normal reaction and how to make a judicious use of the various procedures of regional and spinal anesthesia without apprehension.

I regret that I have not sufficient space to review the general principles of the method of which I have recently published a short review in the *Annals of Surgery*; but although restricting myself to only three topics of regional and spinal anesthesia, I hope they will contain sufficient material to give you a fair picture of the ploughing of that field in which some of us are now reaping wonderful crops.

The dangers attending spinal injections of cocain for surgical purposes led Cathelin, in 1901, to attempt epidural, caudal, or sacral anesthesia, which was placed on a practical footing by L  wen in 1910. Danis, in 1913, described a method of his own by which the sacral nerves could be reached through the posterior sacral foramina forming lateral rows on each side of the sacral spinous crest. These procedures may be used separately or combined to constitute what I propose to call "sacral block."

When caudal injection alone is resorted to 30 c.c. of a 2 per cent solution of novocain containing 10 drops of adrenalin (1:1000) should be used in preference to weaker solutions. The anesthesia sets in less rapidly than in the other forms of nerve blocking, sometimes appearing only after from thirty to forty minutes and resulting only in analgesia which is insufficient for major operations, unless the patient has been strongly narcotized. It is, however, very satisfactory for hemorrhoidectomy, perineorrhaphy provided the labia majora are not clamped too high, cystoscopy including fulguration, and radium treatment of the carcinomatous prostate. For prostatectomy it is not always reliable. L  wen's bicarbonate novocain solution seems to hasten and intensify the anesthesia and to increase its duration.

Transsacral or parasacral anesthesia is obtained by introducing the needle from the rear through the posterior sacral foramina and injecting from 2 to 10 c.c. of a 1 per cent solution close to the nerves as they emerge from the sacral canal. The injection is best made with the

patient lying on his stomach with a cushion placed under the hips. The anesthesia appears very rapidly, almost instantaneously, and lasts for from two to three hours; very often there is no postoperative pain when sensibility returns. Its indications are all operations on the anus, perineum, vagina, prostate, bladder, urethra, and penis. When combined with caudal anesthesia the result is an immediate complete block of all the sacral nerves, and it is considered the method of choice for the Kraske operation.

The foregoing description is but a rough sketch of the picture of caudal, transsacral, or sacral block, and can only appeal to those who are already familiar with these procedures and have used them a number of times; but unless a clear detailed description throws more light on the technic we cannot expect the average physician to make them a part of his surgical equipment. Most surgeons have no time to read fifty odd pages selected from *n* chapters with the sole view of gathering the necessary data for one operation. They should be given every chance to acquire, in a few lines, the special technic which they are anxious to use. But they should also understand that unless they have satisfied the requirements of the method, no satisfactory results will be obtained. Nothing, however, can prevent the younger men in the early stages of their career from mastering the general principles of technic, in order to be able to appreciate the current literature on the subject and to use the method with complete success.

The following important points emphasize an adjustment of certain older principles to our modern technic. The pre-anesthetic and post-anesthetic care of a patient, as well as the proper outfit for inducing regional and spinal anesthesia, should have the special attention of the operator. The education of the patient as well as the control of his psychic condition, on which surgeons are still at variance, are the principal factors leading to success. In localities where the method is used extensively home education is acquired very readily by friends and relatives who have already been operated on by the local method. But in countries where general anesthesia has been the exclusive method employed every patient is anxious to go to sleep as soon as an operation is proposed to him. Nurses should learn how to educate such patients as soon as they are sent to the hospital and should tell them all about the method so that they will know what is expected from them during the operation. It is too late to explain anything during the operation; it only helps to arouse suspicion and apprehension at a time when abso-

lute quietude is desirable. The attendant at the patient's head should know how to use his or her judgment in seeking to divert the patient's attention to some other topic or to leave him alone if he feels sleepy and does not protest. The patient should never be told when the operation begins and such questions as, "Do you feel that?", "Does that hurt?", "How are you feeling?", and so forth, are strictly forbidden because they are suggestive and ruinous to the method. If it hurts he will say so. He only needs encouragement when he is anxious or when the length of the operation begins to be a burden or during a very short stage of painful manipulation.

I must emphasize the necessity for the use of narcotics preceding the anesthesia, but I do not feel inclined to recommend the use of large doses such as would abolish consciousness or impair the general condition of the patient, whose resistance has already been lowered by the disease.

Under the subtitle "preliminary narcotism" Babcock, in 1914, advocated repeated injections of morphin and scopolamin before inducing spinal anesthesia. A first hypodermic dose of one-sixth grain of morphin sulphate and one one-hundredth grain of scopolamin is given one hour and fifteen minutes before the operation, and a like dose is repeated in cases of robust adults, if in twenty minutes after the first injection they answer questions without evidence of mental confusion. A third dose, Babcock says, may be allowed in certain very robust and resistant patients of either morphin alone or combined with one-fifteenth grain of apomorphin "if the delirifacient action of scopolamin predominates." These injections are given at intervals of twenty minutes and are used with great caution. I do not know if Babcock still precedes his spinal injections by such massive doses of morphin and scopolamin, but experience confirms the statement that although these combined drugs constitute the most valuable preliminary adjuvant to any form of anesthesia, they may be reduced without compromising the results of local and regional and even more of spinal anesthesia, which is the block anesthesia *par excellence*. In the majority of cases a single dose of one-sixth grain of morphin and one-three-hundredth grain of scopolamin given an hour before the anesthesia controls the psychic condition of the patient satisfactorily. It is true that narcotics intensify and increase the duration of local, regional, and spinal anesthesia. They facilitate the administration of general inhalation narcotics to such an extent that very nervous patients are able to take the anesthetic easily, are

maintained and controlled without any trouble with a relatively small quantity of anesthetic, even during the longest and most traumatizing operations.

At the Clinical Congress for the Study of Local, Spinal, and Scopolamin-morphin Anesthesia held under the auspices of the Chicago Medical Society, January 26, 27, and 28, 1915, a most interesting discussion took place which ended in the common accord that scopolamin-morphin when used within the limits of safety so as to bring about a semi-waking condition has always given gratifying results.

Experience proves that a weak dose of morphin, one-sixth grain, and scopolamin, one three-hundredth grain, used as a routine procedure is ordinarily sufficient to blunt the consciousness of the patient and eliminate to a satisfactory extent the factors of apprehension and discomfort and allow any operation to be performed painlessly, provided the anesthesia has been induced correctly and every comfort insured on the operating table. Exception should, however, be made when using the sacral block for the Kraske operation during which the position of the patient on the operating table creates more discomfort than the operation itself. I am thus in the habit of administering to those patients my routine dose an hour before the anesthesia and repeating the injection about fifteen minutes before the patient is brought into the operating room. With spinal anesthesia it has not been found indispensable to use the preliminary narcotic, although the psychic condition of women is greatly benefited by the use of the weak dose. Experience has also shown that narcotics should always be given about one hour before the operation if any good results are to be expected. The giving of a hypodermic injection of morphin immediately before the patient is sent to the operating room does not help the induction of anesthesia, whatever the method used. It has been given too late and therefore acts more as an excitant than as a sedative.

Passing on to the anesthetic drug, I wish to state emphatically that novocain is the anesthetic of choice both for regional and spinal anesthesia. It should be pure and freshly prepared. Novocain solutions, contrary to the opinion expressed by almost all writers, lose part of their anesthetic properties by repeated boilings. Novocain hydrochlorid in powder can be sterilized by autoclaving; its melting point is 153 C. Fresh solutions prepared by dissolving sterile novocain in cold sterile normal salt solution are more active.

The addition of adrenalin (1 : 1000 solution) to novocain solutions

is now a routine procedure and its action on the blood pressure is not a novelty; but I wish to call the attention of the medical profession to its use in the future. I was using adrenalin in all my goiter cases (20 drops for each 100 c.c. of the novocain solution irrespective of the strength of the solution) when I came across Goetsch's adrenalin sensitization test which led him to conclude that it is very near pathognomonic for goiter with exophthalmic symptoms. Contradictory findings have been published, but my clinical experience tends to show that we should be a little more cautious in using the drug. I have reduced the dose to 15 drops for each 100 c.c. and do not inject more than 20 drops in the average cases, when more than 100 c.c. of the solution are required. In many instances the poor condition of the heart or the high blood pressure prompts the use of a still weaker dose. For thyroidectomy I still use 10 drops for each 100 c.c. of the 1 per cent solution in paravertebral injections, injecting about 50 c.c., that is, 5 drops of adrenalin in all; but if the patient's condition has been diagnosed exophthalmic goiter, I take the safe side and inject pure novocain.

I confess, however, that I had, before taking cognizance of Goetsch's experiments, used adrenalin in all my solutions irrespective of the nature of the disease.

I am thus led to a *mise au point* of the alleged danger of blocking the phrenic nerve and the vagus when making paravertebral injections of the cervical nerves. Wieman found that for thyroidectomies, when regional anesthesia is induced the day before the operation with a view of determining the exact mechanism of the occasional after-effects resulting from paravertebral injections, roentgen rays in a certain number of cases reveal paresis of the diaphragm on the same side, but without any subjective disturbances. The pulse is sometimes slowed, sometimes accelerated, and sometimes unaffected. The most interesting feature of this experiment is the absence of any trouble at the operation the next day, although the anesthetic is applied on both sides with three or four times as much solution. If the injections are carried down close to the transverse processes laterally, there is very little risk, if any, of blocking the vagus; but it seems to me that the phrenic nerve is anesthetized in every case, although not to such an extent as to paralyze the diaphragm; even then the intercostal and other respiratory muscles compensate for the functional deficiency of the diaphragm.

During the years 1919 and 1920, some very interesting work has been done on the anesthesia of the abdominal cavity and its content.

The difficulty encountered in handling painlessly the diseased viscus after laparotomy under local anesthesia of the abdominal wall had already given rise to the paravertebral conduction method in order to obtain a wider anesthetic field on which the surgical maneuvers would not create too much discomfort to the patient. It was necessary to inject from the fifth dorsal to the second or third lumbar nerves on both sides, that is, twenty to twenty-two nerves (Kappis) or from the seventh to the twelfth dorsal nerves (Labat), that is, twelve nerves. In the latter case, the diffusion of the solution to the adjacent upper and lower nerves probably accounts for the success notwithstanding the difference between the two procedures. Finding this method tedious to the operator and trying to the patient, a certain number of experiments were conducted with a view to finding a simpler method.

In 1913, Kappis made extensive experiments on dogs with a view to throwing some light on the existing conflict of opinion regarding the sensory distribution of the abdominal cavity and its content. Excluding the use of narcotics he tried to determine what pain it would be possible to induce by irritating the intestines. He divided his experiments into two parts, first, a preliminary, and second, an examining operation. Sections of the cord were made at different heights, sections of the abdominal wall along the costal margin, and the results of his experiments were the following: after sectioning the cord between the fifth dorsal vertebra and the sixth dorsal vertebra there was no pain in the abdomen. After sectioning the cord between the seventh dorsal and eighth dorsal vertebræ there was no pain in the lower abdomen up to the middle of the small intestine; but the stomach, spleen, and upper part of the small intestine were found sensitive. Between the thirteenth dorsal and the first lumbar vertebræ (the dog has thirteen dorsal vertebræ) sensibility stopped at the cecum. Kappis concluded, therefore, that below the cecum all organs are supplied by lumbar and sacral nerves. This is confirmed by my clinical experience that the blocking of the last three lumbar nerves and the five sacral nerves gives a complete anesthesia of the pelvis and its contents.

The sectioning of the splanchnic nerves done by Kappis gives an anesthesia of the stomach, spleen, and upper part of the small intestine. The liver seems to bear an embryologic relationship to the gastrointestinal tract. The kidney was not deprived of sensibility after sectioning the splanchnics, which proved that at least part of its sensibility originates from the lumbar spine. In 1919, Kappis published

another very interesting contribution, which adds to the knowledge obtained from his papers of 1913, that the first three lumbar nerves send rami-communicantes to the retroperitoneal ganglion and therefore take part in the transmission of pain from the upper abdominal organs below the colon sigmoid whose sensory innervation ends with the third lumbar nerve. The sensory innervation goes through the hypogastric plexus to the rectum and to the urogenital apparatus.

Hoffman's clinical findings published in 1920 confirm to a certain extent Kappis' experiments proving that sectioning of the spinal nerves supplying the abdominal wall is not followed by an exclusion of painful impulses which are always present in the mesentery. He also found that the sectioning of the splanchnic nerves abolishes pain, and is of the opinion that these findings can be applied to man. Hoffman goes still farther in contending that there is no difference in pain sensation between the cerebrospinal and vegetative nerve systems, which is contrary to the opinion of Lennander, who holds that no sympathetic fibers are able to transmit pain. Hoffman says that both systems have the same centripetal tracts; that they transfer the same conscious sensibility and that they have a unit embryologic history; that the sensory nerves lie in the parietal peritoneum, mesentery, and lesser omentum, and that these organs are the starting point of abdominal pain. He made sections of the peritoneum and used the method of Bielschowski modified by Schultz and Gross in which nerves are tinted black and easily seen. Vessels are sometimes stained by this procedure, but good pictures of nerve ramifications are usually obtained by which it is easy to distinguish the nerves from the blood vessels. Sensory nerve fibers were found to accompany the vessels of the mesentery and also those of the parietal and visceral peritoneum. Certain regions between two vessels contained no nerves. Clamping two adjacent vessels of the mesentery produced pain, and in treating this region by the above process it was found that the clamped vessels contained nerves coming from the splanchnic or sympathetic chain. Dissections also showed that the splanchnic nerves had fibers running to these clamps.

Kappis does not deny the presence of nerve plexuses supplying the viscera and containing sensory nerve fibers, especially pain conducting fibers. Their number is relatively small as compared to the extent of the viscera supplied, and for this reason they lose their ability to transmit painful impulses in the proximate vicinity of the organ itself. It may be that these fibers do not reach the organ with the other nerves,

but end at a certain distance from it, it may also be that they do not reach the organ in such number and size as to permit of impulses being interpreted as pain. Clinically, abdominal organs are insensitive.

Consequent upon the above findings it was thought rational to try the anesthesia of the splanchnic nerves and that of the rami-communicantes given off by the first three lumbar nerves. A posterior route of approach was studied on the cadaver and applied to the patient, which has given, in the hands of Kappis, Naegeli, Hoffman, and myself, satisfactory results, especially in very lean patients. The solution diffuses sufficiently in the retroperitoneal tissue to secure at the same time the anesthesia of the cerebrospinal nerve plexuses lining the posterior wall of the abdominal cavity under the direct influence of the operative maneuvers. The technic is simple and safe and should be tried as often as possible in abdominal surgery.

I should like to approach the question of spinal anesthesia, not with the view of discussing the methods already employed on the continent and in America, but of presenting a technic I have been using for the last three years without any untoward effects and I may say no failures. The practice of dissolving the anesthetic drug in cerebrospinal fluid for the purpose of intraspinal injection is not new, but the many little details attending the injection of such a solution are those to which I wish to call your attention, since my impression is that the absence of one or more of them is likely to bring about troubles ranging from the simple headache to the occasional cessation of respiration. Briefly, my technic is as follows:

The patient is injected in the upright position as usual. The puncture is made at any level between the twelfth dorsal and the fifth lumbar vertebræ according to the height of the anesthesia desired. No attempt is made to produce anesthesia higher than the line of the nipples. After making the puncture the first few drops of cerebrospinal fluid are allowed to flow out so as to obtain a clear fluid which is allowed to fall in a special ampule containing the anesthetic drug. More fluid is withdrawn, varying between 10 and 25 c.c., according to the condition of the intraspinal pressure which very often agrees with the blood pressure. The appearance of headache should prompt the cessation of further withdrawal of fluid. The solution thus made is aspirated into any kind of syringe by means of a spare needle, the syringe is then adapted to the spinal puncture needle, and as much new fluid is brought into the syringe as it now contains solution. Half of this is injected

very slowly, more new fluid is aspirated, the syringe is discharged in the same way, leaving less and less fluid in it, and at the end of four or five injections it is emptied. There is no hurry in placing the patient in the recumbent position, but there is also no reason for keeping him in the erect position. He is, therefore, placed on his back, and by the time the operative field is prepared he can be placed in the Trendelenburg position and stay there until sensibility returns without prejudice to his respiratory function. As is usual with spinal anesthesia the blood pressure falls in the majority of cases very rapidly affecting only the maxima and comes back to normal later, sometimes during the operation and sometimes only in the afternoon, without changing the clinical aspect of the patient whose condition he, himself, considers to be very satisfactory. The minima is but little affected. No postanesthetic headache, nausea, or vomiting has been observed following 110* spinal anesthetics given in the Mayo Clinic since my arrival October 2, 1920. A nauseated condition sometimes exists, especially with the Trendelenburg position, which disappears rapidly by deep breathing. No special postanesthetic care nor position was especially indicated in the patients thus anesthetized.

I am familiar with Barker's and Babcock's solutions and technic. After using stovain, cocain, and a combination of cocain and novocain, in varying doses, I have adopted novocain in doses of 0.10 gm. and 0.12 gm., according to the body weight of the patient. One centigram for each 15 pounds of body weight has clinically proved to be a safe dose and produces satisfactory anesthesia for a period varying from one hour to one hour and a half. No adrenalin is added to the novocain, which should be chemically pure and sterile. Adrenalin is here of no use since its action on the blood vessels is of no avail in the spine.

The necessity for making the injection as slowly as possible is to keep the solution in the close vicinity of the site of puncture and allow the nerve structures to take up the greater part of the anesthetic, leaving a dose too weak to produce anesthesia by diffusion higher up. The anesthetic fluid acting as a dye impregnates the nerve tissues more deeply at its first point of contact.

After withdrawing a certain quantity of cerebrospinal fluid the intraspinal pressure decreases while the secretion and excretion of more fluid has to take place in order to make up for the deficiency created by the withdrawal of such fluid, so that if the intraspinal injection is made very slowly there is no reason why the injected solution should ascend

* The number has since greatly increased.

toward the head. The normal circulation of cerebrospinal fluid also helps the injected solution to flow toward the blood circulation, that is, toward the periphery. I do not consider the cessation of respiration which might happen in such cases to be due to the direct action of the anesthetic fluid on the respiratory centers by diffusion up the spinal canal; but its passage in the general circulation is probably the cause of such trouble when too heavy a dose has been administered. Without exerting great pressure while making the injection, the anesthetic fluid does not ascend toward the head when using cerebrospinal fluid as the solvent of the novocain. Patients placed in the Trendelenburg position for one hour do not show anesthesia of the upper extremities, thus indicating that no solution, at least no active solution, reached the emergence of the roots constituting the brachial plexus. The spine cannot be considered as a test tube and all experiments *in vitro* cannot be applied to the human spine unless rough handling of the technic disturbs the physiology of its contents. The disturbance of the content of the subarachnoid space may be compared to that of a vessel containing water, whether still or circulating, when a stone is thrown into it (the injection representing the stone), ripples will be formed which represent the injection waves; the heavier the stone, the greater the disturbance and the larger the ripples, the greater the pressure with which the injection is made, the greater also is the intraspinal disturbance and likewise the injection waves, which then might reach the head.

LeFilliatre was the first to induce general anesthesia by means of spinal injections made as low as between the fifth lumbar vertebra and the sacrum. His technic is based on the fact that great pressure is capable of running the solution up toward the head, thus producing general anesthesia.

The conclusion must be reached that pure sterile novocain dissolved in cerebrospinal fluid in doses of 0.01 gm. for each 15 pounds of body weight of the patient is safe, provided the injection is made very slowly.

I have not seen any contraindication to spinal anesthesia with the technic I use, unless it is in patients whose blood pressure is below 100. Even then, if the condition of the patient does not allow him to have any other form of anesthesia, I would not hesitate to use spinal anesthesia, injecting at the the same time subcutaneously spartein sulfate, 1 grain, caffein, 4 grains, and strychnin sulfate, one-sixtieth grain, repeating the dose, if necessary. Patients suffering from fibrillation of the auricle have behaved themselves very well under spinal anesthesia when operated on for diseased gallbladder or prostate.

CONCLUSIONS

Regional anesthesia, in which should be included spinal anesthesia, has developed into a science and should be treated as such. To be successful the anesthetist should have a perfect knowledge of anatomy and surgical technic, and should be familiar with the chemistry, pharmacology, and the physiologic effects of the drugs he administers. He should know how to handle the patient before and during the operation and, above all, he should have mastered the general principles of the methods.

The surgeon who operates under regional anesthesia should be familiar with the general principles of the method so as to be able to complete the anesthesia during the operation. He should not have to resort to general anesthesia when one or two injections judiciously made would render the operation painless. Such knowledge would also give him a correct idea of the extent of the anesthetic field and in a general way help him to understand the after effects, if any, and the treatment thereof.

The beginner should not be expected to be successful with his first attempts, partial failures can be remedied by inhalation narcotics. He should not abandon the method as being worthless or insufficient. He should remember that even experts may fail and should try it again, observing scrupulously its principles until he succeeds. There is no reason why he should not succeed when in the hands of others the results have been so satisfactory. But he can readily understand from the foregoing how necessary it is to have an exact knowledge of the technic and attending circumstances of spinal anesthesia if he wishes successfully to employ such a delicate procedure.

Novocain is the anesthetic drug of choice in both regional and spinal anesthetic procedures. It should be pure, and when injected intraspinaly, pure and sterile and dissolved in the cerebrospinal fluid of the patient. The dose of 0.01 gm. of novocain for each 15 pounds of the body weight of the patient, injected very slowly, is safe for any operation below the diaphragm.

May I at the end of this paper suggest that every young medical student should devote part of his time to studying this method so as to be able to apply it later on in his own private practice. And since a knowledge of general surgery is required, he who is anxious to make it a specialty should have a postgraduate course in that subject.

THE VALUE OF RADIUM AND ROENTGEN-RAY THERAPY IN HODGKIN'S DISEASE*

HARRY H. BOWING

The symptoms and course of Hodgkin's disease may be modified favorably by the application of radium and deep roentgen-ray therapy. Many patients with Hodgkin's disease have been successfully treated at the Mayo Clinic with the technic described in this paper. The primary result is of foremost importance in this discussion, since there is not time to present details with regard to the after result. Reduction in local and distant glandular masses and general systemic improvement are noted in practically all cases, and it is reasonable to conclude that the expectation of life has been increased.

Hodgkin's disease is an infectious granulomatous process involving the lymphadenoid tissue of the body with early enlargement of the cervical glands. The superficial and deep lymphatic enlargements are gradual, progressive, and painless, and produce anemia or are associated with it, hepatauxe, and splenomegaly with or without fever. Death may occur in a few months or the disease may extend over a period of several years.

Etiology.—Although the specific etiology of the disease is not known, Trousseau and Bunting and Yates have demonstrated that focal infection plays a definite part. The origin of the infection may be tonsillar, dental, or in the accessory sinuses. The patient usually volunteers the information that the glandular enlargement followed an attack of influenza, a "head cold," and so forth.

Hodgkin's disease is widespread in the United States and in Europe. There is no special geographic distribution and no race immunity. In a group of 122 cases Bunting has shown that males are twice as susceptible as females. Although it is a disease of youth and early adult life, it may attack persons of any age. With a careful technic diphtheroids may be cultured from the glands. Negri and Mieremet, Bunting and Yates,

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and Rosenow have isolated these organisms. Inherited tendencies or direct contagion cannot be proved.

Pathology.—There is a gradual enlargement of the superficial and deep glands and of many organs containing lymphoid foci. The primary lesion is usually in the cervical glands with extension to the axillary glands on the same side. The opposite cervical, axillary, and inguinal groups of glands are then attacked. Many of the lymphoid foci of the body may also enlarge. The primary lesion may appear in the gastrointestinal lymphoid apparatus or in the spleen. The glands are encapsulated. They do not metastasize or show any vegetative characteristic, although they have the malignant characteristic of recurring after operation or radium and roentgen-ray treatments.

The glands do not become so enlarged as those seen in cases of lymphocytic leukemia. They are spherical or oval in form and are never fused. The enlargements remain discrete, but may be intimately bound together by a chronic periadenitis, the end process resembling a huge mass. The consistency of the glands varies. The cellular hyperplasia, characteristic of the early stage, shows the glands to be soft, but not so medullary as those of leukemia. In the late stage, due to fibrous changes, they become firm and hard.

The predominance of lymphocytic proliferation in the microscopic picture has led most observers to conclude that the process is inflammatory, the result of some irritant. The glandular enlargement, however, may be the result and not the cause of the disease.

The proliferation of the reticulo-endothelial cells and fibroblasts is the most characteristic change in the process. The gland's architecture is lost early. The stimulation is soon followed by a destructive reaction, reducing the number of the lymphocytes in the glands and, as Bunting and Yates have pointed out, in the blood stream. Diffuse sclerosis occurs as a fibroblastic change in the glands, but does not attack the capsule as in nonspecific chronic lymphadenitis.

The most important single feature in the microscopic pathology is the atypical proliferation of endothelial cells leading to giant-cell formation. The cells are present in all cases, but vary in number. If the lesions progress, sclerosis increases and the gland is gradually replaced by dense fibrous tissue.

Blackford's summary is similar to that of Dorothy Reed; proliferation of large endothelioid cells; production of numerous multinucleated giant-cells; progressive fibrosis, and abundance of eosinophilic cells.

Symptoms.—For therapeutic purposes the cases may be divided into two groups: the acute and the chronic. The acute condition is characterized by very rapid progression of all the features of the disease and is usually associated with intermittent fever. If fever is present, it is moderate, whether or not the glandular enlargement is marked, and lasts for from ten to fifteen days. Glandular swelling is usually the first sign, although recently the patient may not have felt as well as usual. Malaise and weakness are more or less constant. Periods of increase in glandular swelling alternate with periods of remission and the patient usually feels improved. The glandular swelling is painless, beginning in the cervical group with extension to the axillary, inguinal, and later to the mediastinal or abdominal lymphatics. One or more cervical glands on one side of the neck are usually affected first; later the growth extends in the same group and then into the opposite cervical group.

Many clinicians believe that superficial glandular enlargement is associated with a similar enlargement of all the lymphoid structures of the body. Anemia is usually moderate and steadily progressive, although seldom extreme. The huge glandular enlargements may produce edema, and difficult motion of the head, arms, and legs. An intense generalized pruritus may be present. The acute condition seldom becomes chronic; it extends over a period of a few months, terminating in death.

Chronic Hodgkin's disease is similar to the acute condition except that it varies in intensity and duration. Pressure symptoms from involvement of the deeper group of lymphatics occurs usually in the late stage. The bronchial and mediastinal glandular enlargements cause an irritative productive cough, pains in the chest, intense dyspnea, dysphagia and cardiac embarrassment, with enlargement of the superficial veins of the anterior chest wall.

The abdominal enlargement may be primary and associated with jaundice and edema. The pain is usually a dull ache in the lumbar region, occasionally across the lower abdomen, and may be referred down the legs. The anemia increases steadily, although remissions are common. Malnutrition may be present. Fever, which is variable, is usually moderate and resembles that of pulmonary tuberculosis. The disease is usually a termination of intercurrent infection, acute tuberculosis, anemia, and so forth, or of a general decline resembling toxemia. There are many variations in these groups, the controlling features of

which are unknown. The portal of entry and personal resistance probably play an important part. Many cutaneous lesions resembling inflammatory processes have been reported and described as definite nodules of Hodgkin's type and similar to the nodules of leukemia. The pruritus is usually generalized, intolerable, and resistant to ordinary treatments. The blood changes are not constant.

Differential diagnosis.—Hodgkin's disease, lymphosarcoma, tuberculous adenitis, and pseudoleukemia have certain symptoms and signs in common, although each has a distinct clinical course and pathologic picture. The differential clinical diagnosis in early Hodgkin's disease, lymphosarcoma, and tuberculous adenitis is difficult and almost impossible. The blood picture of leukemia gives a clue to this condition. The process in Hodgkin's disease is slower than in sarcoma and usually occurs before the age of thirty-five. In early cases of lymphosarcoma a differential diagnosis is impossible, although the condition usually occurs after the age of thirty-five. Extraglandular infiltration of the surrounding tissue with fixation of the mass is usually present. Tuberculous adenitis is considered a disease of youth. Diagnosis in the early cases is very difficult, although, if the condition progresses, there may be an associated extensive softening and caseation.

In pseudoleukemia the glandular enlargements are more widespread and are usually soft and medullary. The blood picture serves as a basis for the diagnosis. Radical surgical treatment of Hodgkin's disease may be considered, although an isolated gland should be excised and submitted to pathologic examination.

Prognosis.—In untreated cases of Hodgkin's disease, the acute condition is fatal within a few months, while the chronic phase may endure for from two to five years. The condition is uniformly progressive with latent periods and an associated feeling of good health. There are no reported cases of spontaneous recoveries.

Radium technic.—One thousand milligram hours of radium are delivered to areas of skin each 3 by 4 cm. covering the involved glands. The number of areas is dependent on the amount of involvement. Fifty or 100 milligram doses of radium salt or emanation are contained either in a universal tube applicator, with silver walls 0.5 mm. thick, or in a brass capsule of equal density. The radium is maintained 2.5 cm. from the skin, being filtered through the wall of the applicator and 2 mm. of lead. The duration of radiation is twenty and ten hours respectively for the silver and brass applicators. To maintain distance, gauze or wood

(Balza) has been used. This wood has been used satisfactorily at the Mayo Clinic for the last three years, as it is light, soft, and inexpensive. A disk of lead 3 by 4 cm. and 2 mm. thick is placed on the top of the radium applicator to complete the package. Adhesive plaster is used to strap the parts of the block together and to fix it to the patient.

If the top surface of the applicator should come within 2 or 3 cm. of the adjacent skin surface, it is thoroughly protected with a sheet of lead 1 mm. thick. Interposed between the lead and the surface of the skin is a sheet of rubber 1 mm. thick which absorbs the soft secondaries from the lead sheet; this extends 1 cm. beyond the edge of the sheet of lead.

Treatment.—From 5,000 to 6,000 mg. hours of radium are applied to each right and left cervical and to supraclavicular areas, from 2,000 to 3,000 to the infraclavicular and inguinal areas, and from 1,000 to 3,000 to the axillary areas. Any palpable abdominal glandular enlargement is blocked off in a manner similar to that described for the cervical area. Mild reactions, such as malaise, anorexia, nausea, and occasional vomiting, are usually disregarded; severe reactions are avoided. Should a severe reaction occur, the radium treatment is usually abandoned for a period of from two to three days or until the patient returns to a satisfactory condition. The fluid intake and elimination are usually encouraged and soda bicarbonate is given in dram doses three times a day.

Two to four areas are usually radiated at one time with an interval of two or three days between treatments. A mild or intense erythema may occur after the last application or two or three weeks later. It yields readily to ordinary treatment and lasts for from three to ten days. The part should be kept dry and dusted freely with a good grade of bland impalpable dusting powder. No secondary skin changes are noted, although the natural skin pigments may be increased; this does not necessarily follow an erythema.

Roentgen-ray technic.—Formerly many patients with Hodgkin's disease at the Mayo Clinic were treated by the formula as follows: A broad focus Coolidge tube, a 23.7 cm. parallel spark gap, skin target 22.8 cm. distance, time six and one-half minutes, 5 ma. of current, filtration 3 mm. of aluminum, and a piece of sole leather. Multiple portals of entry varying in size were used. Treatments were repeated at intervals of three weeks until a series of six or eight had been given. In our present formula the distance has been increased to 30.5 cm. from the skin, time twelve minutes, filtration 6 mm. of aluminum, and a piece of sole leather. The number of portals of entry is limited. One area of

both the right and left cervical regions is exposed. The chest is equally spaced in four squares; the size of the opening depends on the size of the chest wall. One area in both the right and left axilla and one area both in the right and left inguinal glands are exposed. The back is divided into eight areas. The upper and lower limits are marked respectively by transverse lines at the level of the seventh cervical vertebra and gluteal fold of the buttock. Treatments are repeated every three weeks until a series of six or eight have been given; an interval of three months is allowed to determine whether or not further therapy is indicated.

The roentgen-ray treatments are usually given at the beginning or at the end of the radium exposures. Irradiation of the anterior abdominal wall is avoided, since it may result in very severe reactions, which resemble peritonitis, with marked distention of the abdomen and ileus, associated with abdominal pain. There are frequent foul smelling, greenish stools. Convalescence extends over a period of six to ten weeks. Mild reactions similar to those following radium applications may occur from roentgen-ray exposures of the chest and back.

The two great body cavities and all possible superficial glandular enlargements should be treated with the roentgen ray at the onset of the disease in order to ward off the impending mediastinal and abdominal enlargements, if possible. The initial good results of radium and roentgen-ray therapy may be due to the direct destructive effects on the glandular enlargements characteristically composed of an abundance of nuclear substance, lymphoid elements, endothelial cells, and so forth. The large glandular endothelial cells are very susceptible to radiation. Fibrosis, which is nature's method of recovery, is set up by radium and the roentgen ray.

Treatment should be instituted as soon as possible. The anemia should be treated with the ordinary therapeutic agents and all possible foci of infection removed. If the anemia is steadily progressive, radium and roentgen-ray treatments should not be given too intensively because of the destructive effect of irradiation. Vaccine and serums are of doubtful value.

CONCLUSIONS

In early cases of glandular enlargement, an isolated gland should be removed for examination by a pathologist. The life expectancy of the patient should be increased by intensive radium treatment of the superficial glandular enlargements and deep roentgen-ray therapy of the

thoracic and abdominal cavities whether or not the roentgenograms are positive. Huge glandular enlargement and mediastinal involvement are markedly diminished. The generalized pruritus may diminish and in some cases may entirely disappear.

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RADIUM AND ROENTGEN-RAY THERAPY IN MALIGNANCY: INDICATIONS, CONTRA- INDICATIONS, LIMITATIONS, AND RECENT DEVELOPMENTS*

ARTHUR U. DESJARDINS

The use of radium and roentgen rays in the treatment of certain diseases is gradually assuming a more and more important place in medicine. This is particularly true of malignant conditions, in the treatment of which radiation bids fair to become increasingly important. Unfortunately the proper evaluation of these agents, like all other therapeutic agents in their early days, is being made more or less difficult by the usual troubles of youth and by more or less exaggerated claims bringing forth, from the less interested members of our profession, indications of a skepticism which, even if at times partly unwarranted, is bound in the long run to help us maintain a more judicious and more sanely critical attitude toward our work.

If we wish our progress to be steady and as free as possible from the missteps and reversals which have marked the development of every branch of science, we must base our practice on sound principles and formulate our technic from information laboriously and patiently obtained by the physicist, the biologist, and the pathologist.

Before considering more in detail the use of radium and roentgen rays in the treatment of malignancy, I should like to emphasize briefly certain well known fundamental factors, the importance of which is not always sufficiently realized. Some of these factors impose on us limitations that we are constantly striving to overcome.

INVERSE SQUARE LAW

As we know, therapy by radiation is absolutely dominated by the inverse square law, the practical importance of which is so great that in making any application of radium or roentgen rays, it should automatically become the radiologist's first consideration.

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For example, if a tube of radium is placed with relation to a malignant growth the intensity at points 0.5, 1.0, 5, and 10 cm. respectively from the tube will be 1, 0.25, 0.01, and 0.0025 (taking as a unit the intensity at 0.5 cm.). If the dosage was correct for a distance of 5 cm. from the tube, it must follow that the portion at 0.5 cm. will be burned by a dose one hundred times too great, while the portion at 10 cm. distance will receive little or no therapeutic effect. In principle, this law applies to both radium and roentgen rays. While this difficulty cannot be overcome completely, its consequences can be avoided to a considerable extent, as far as roentgen rays are concerned, by increasing the distance between the tumor and the source of radiation. We can thus minimize the difference between the intensity of the rays as they enter the proximal surface of the tumor and as they leave the distal surface. In other words, the different parts of the tumor will receive a more uniform quality of radiation. However, the associated disadvantage is a great loss in the total intensity available, a loss which must be compensated for by a great increase in the time of exposure.

Another way of avoiding the consequences of the inverse square law is to increase the number of sources of radiation; this may be accomplished by multiplying the number of areas treated. In this way as many multiples of a single dose may be concentrated into a limited internal area as the number of different superficial areas through which the treatment can be given. This latter method should be selected in treating a tumor situated at approximately equal distances from two opposite surfaces of the body. In some cases a combination of the two methods may be advisable or necessary. However, should the tumor be superficial, increase in focal distance alone is to be preferred as a means of increasing the dosage delivered to the tumor. Such increase in distance should, of course, be adequately compensated for by increase in time of exposure.

The only way to overcome the handicap of the inverse square law with any degree of effectiveness in the case of radium is by burying the radiation units in the tissues and increasing the number of those units. This may be accomplished by inserting into the tissue tubes of radium or its emanation which are allowed to remain in place either temporarily or permanently. However, because of the short and rapidly decreasing period of activity of radium emanation; because of the necessity of leaving in place the small glass containers; but particularly because of the intense necrosis produced around such unfiltered radiation elements,

the use of buried emanation, while undoubtedly of great value in many cases, will probably be gradually replaced, at least to some extent, by the use of radium needles containing a definite quantity of radium salt of stable activity. These needles, with varying degrees and qualities of filtration, aid in avoiding some of the tissue necrosis occurring around an unfiltered glass emanation unit. Such necrosis is definite and complete within a zone, the extent of which is proportionate to the radium content of the tube.²

The question of filtration is becoming more and more important. We know that the rays from a roentgen-ray tube or from a radio-active substance, such as radium or its emanation products, are not homogeneous; that is, they are not made up of rays of one wave length. On the contrary, such rays are extremely heterogeneous, being composed of a mixture of rays of all wave lengths. The longer, being easily absorbed or weak in penetrating power, do not pass beyond the first layers of tissue cells, while the rays of shorter wave lengths penetrate deeper and deeper into the tissues. This complex character of roentgen rays and radium rays, to which their unequal absorbability is due, constitutes another major limitation in efficient therapy by radiation, a limitation almost as great in its effects as the inverse square law. Such limitation may be minimized to a considerable degree by filtration. In treating a malignant tumor with roentgen rays attack must generally be made through the skin or mucous membrane, both of which are extremely sensitive to so-called soft rays, or rays of long wave length. This fact has brought grief to many radiologists in the past, and we still occasionally are reminded that the skin will withstand only a limited degree of insult. By adequate filtration wave lengths least injurious to the tegument can be selected. In other words, the softer rays are absorbed by the filter which prevents them from injuring the skin or mucous membrane. Another very important point is accomplished; that is, an increase in the homogeneity of the effective radiation, or rather a decrease in its heterogeneity.

The situation with regard to radium is quite different. If we wish to treat a lesion by external application we must use heavy primary and secondary filtration in order to avoid serious burns. One millimeter of platinum or its equivalent will filter out all the β rays and the less penetrating portion of the γ rays. Two or three millimeters of rubber will eliminate the secondary rays generated by the primary radiation in the metal used as a filter. If we wish to attack a lesion by burying in it

radium or its emanation, filtration may not be necessary, especially in tumors of relatively small size. Around each unit of radium or its emanation so placed there occurs destruction in the form of necrosis which may be more or less extensive according to the dosage. Beyond this zone of necrosis, the tissue constituents of which act as a filter, a so-called selective effect is obtained. The tissue adjoining the radioactive substance filters out the softer, less penetrating rays, to which the necrotic effect is due, and the effect of that portion of the radiation which has gone through this zone unabsorbed then depends on the radiosensitiveness of the tissue cells outside that zone. When buried emanation is used the zone of destruction is greater because nearly all of the β and γ radiation passes out of the glass tube; whereas with platinum needles, or other filters of relatively high density which allow the escape of only the more penetrating portion of the β and γ radiation, the zone of destruction is more limited.

By far the most serious limitation in the diagnosis and treatment of pathologic lesions springs from the fact that we must depend almost entirely on our human eyes and hands. These are very gross instruments and, even with very effective therapeutic agents, we can never hope to accomplish the cure of more than a certain proportion of the malignant diseases we may undertake to treat. Those of us who have had experience with pathologic conditions found at necropsy know but too well the uncertainties and deceptions of our methods of physical diagnosis. Some consolation may be derived from the fact that the radiologist's limitations in this respect are shared equally by the surgeon and the internist. It is a very common occurrence to find that a malignant lesion supposedly limited to a certain organ or tissue had actually become much more widely disseminated either by direct extension, by metastasis, or both. The only way we have of combating this limitation is by impressing on the public and members of the profession in general the extreme importance of early diagnosis and treatment. Although something can be accomplished in this direction, the very limitation in the acuity of our senses often makes an early diagnosis in the first instance difficult. It is not unusual to be told by patients that, when they first consulted a physician concerning a lesion which appears to have been an early manifestation of a malignant process, they were told that it was of no significance and that they should promptly forget it. Such instances influence us to conclude that physicians are as much in need of "education" as the public in this most important matter.

INDICATIONS AND CONTRA-INDICATIONS FOR RADIUM AND ROENTGEN-RAY THERAPY

Our first consideration must be the diagnosis; because, if we are to utilize radium or roentgen-ray therapy with any degree of success, we must know the nature of the lesion we wish to treat. Not only should we know the type of malignancy, but as many as possible of its salient features; such as the predominating type of cell, and reaction factors. It is not always possible, nor in some cases is it necessarily advisable, to obtain such complete information. Judgment should be applied to the individual case. The lack of a definite diagnosis constitutes a fundamental contra-indication to such treatment. The other important contra-indications are:

1. The bad general condition of the patient, making it impossible or dangerous to administer really adequate treatment.

2. Tumors complicated by infection. This condition is not infrequently encountered, especially in association with carcinoma of the uterus, but occasionally also in other locations, such as the breast. In such cases drainage and other general measures must be instituted before radiation.

3. Lack of suitable apparatus, or the knowledge requisite for its proper use. We occasionally still hear of physicians attempting to treat malignant conditions with such facilities as are provided by an ordinary portable bed-side unit.

Radium is particularly indicated when we are dealing with a fairly small lesion or tumor at or near the surface of the body (or reasonably accessible from the outside), the extent of which can be outlined with a fair degree of accuracy. Its ideal indication is in conditions in which it is possible to introduce the agent into the substance of the lesion in such a manner as to deliver to every part fairly uniform radiation in adequate dosage.

At the present time radium, alone or in conjunction with roentgen rays, is indicated and should be used preferably by the needling method, in cases of solitary glandular carcinoma or sarcoma of limited size and well defined extent especially on or near the surface of the body and in cases of solitary or discrete, superficial, malignant gland or cutaneous metastasis. Malignant conditions in cavities accessible from the body surface (uterus, vagina, rectum, bladder, mouth, nose, larynx, and esophagus) should preferably be treated with radium or its emanation,

usually in conjunction with external roentgenization. In cancer of the uterine cervix, for instance, radium achieves marvelous results in many cases because the element can be introduced into the cervical canal and is there surrounded on all sides by the neoplastic tissue. From our present knowledge the method of employing therapy by radiation to the best advantage in such conditions would seem to lie unquestionably in the combination of radium internally and roentgen rays externally.

The γ rays of radium are more penetrating than the roentgen rays used at present for therapeutic purposes. Experimentally, roentgen rays have been produced with wave-lengths as short as some of the γ rays, and these may be available before long. However, with the small dosages commonly used, the total radio-active energy delivered to a lesion or tissue beneath the surface is very small, and constitutes an extremely small fraction of the total radiation generated by a given quantity of radium. Furthermore, our present means of employing radium for therapeutic purposes are such as to make it impossible to deliver uniform radiation to a lesion of any extent on the surface. This difficulty is magnified many times when we are dealing with a deep lesion the exact extent of which cannot be outlined accurately. These factors determine in a very large measure the indications for the use of radium or roentgen rays.

Roentgen rays act at a more uniform intensity over a much wider field than radium rays. Although their intensity decreases rapidly as they pass from the surface to deeper and deeper tissue layers, a portion of this loss can be compensated for by increasing filtration, focal distance, and the number of so-called ports of entry. Therefore, if we are dealing with an extensive superficial lesion or with a lesion, either superficial or deep, whose exact extent cannot be fairly accurately outlined, roentgen rays are the agent of choice. Tumors with a tendency to metastatic dissemination by way of the lymphatics or growths in which metastasis is suspected or to be expected, should be treated either by roentgen rays alone or combined with radium, such as the neck with its complicated lymphatic system in malignancy of the mouth or face and the thorax and axilla in cancer of the breast.

Combination of roentgen rays and radium.—Although the indications for roentgen rays or radium are usually quite well defined, there are many cases in which both should be used in conjunction. As a matter of fact, the ideal method of treating many malignant tumors is by a

judicious selection or combination of surgery, roentgen rays, and radium. In selected cases, surgery should be a preliminary step to prepare the field and to permit direct visual application of the radium, to be supplemented or not by roentgen radiation. If anything really substantial is to be accomplished in the therapy of malignant conditions by radiation, our procedure must be based on one essential requirement. The entire involved area with its lymphatic drainage must receive a uniform lethal dose, which should be delivered, as nearly as possible, during the first treatment. I do not mean to imply that it is necessary to give such dosage at one séance, but the treatment should be completed within as short a period as the condition of the patient and the degree of reaction will allow. To scatter a course of treatment over a period of weeks is to defeat the very purpose we are attempting to achieve. If involvement is limited and it is reasonable to expect a cure, we should aim to destroy the malignant elements by one attack. As heavy dosage as the integrity of important neighboring structures will allow should be administered with adequate filtration in order to minimize as much as possible the deleterious effects of the long wave length portion of the radiation. Limited radiation with limited dosage is to be used when a cure is out of the question and only palliation is to be expected.

The importance of treating the lymphatic system draining the area of a malignant tumor cannot be overemphasized. Untreated elements not uncommonly show signs of activity. This is of especial importance in carcinoma, the dissemination of which takes place so largely by way of the lymphatic system. Although this consideration might seem self-evident the manifest lesions only are often treated in a scattered fashion and the lymphatic drainage system overlooked. In fact, in most malignant conditions the lymphatic drainage system should be treated before attacking the main lesion. In general, we should adopt the same procedure in sarcoma, although in these cases dissemination by way of the blood stream is the rule. The anatomy and physiology of the circulatory system and the general pathologic features of carcinoma and sarcoma enable us to understand why in the former metastasis usually takes place through the lymphatic system, but in the latter occurs by way of the blood stream.

Sarcoma, especially sarcoma of bone, has a very great tendency to metastasize to the lungs.¹ It is difficult to say why this is true. There seems to be very little doubt that the dissemination of metastatic ele-

ments or emboli takes place quite early and the reason many of these do not lead to gross secondary lesions possibly is due to the activity of some defensive mechanism elaborated in the body fluids as the result of the antigenic action of the primary growth. An explanation of the fact that metastatic elements which give rise to secondary lesions have such a predilection for the pulmonary organs may perhaps be found in the fact that the pulmonary circulation constitutes the first capillary bed through which the blood from the general circulation passes.

Whatever may be the truth with regard to metastasis the questions arise: Should we make it a routine practice to radiate the mediastinum and lungs in sarcoma in the hope of destroying metastatic deposits, even if not demonstrable? Should we radiate the mediastinum and lungs at all? Should we treat only these organs or should we attempt to radiate the entire trunk on the basis that, while pulmonary metastasis is the most frequent site, metastasis not infrequently occurs in other organs?

In a recent personal communication, Bloodgood writes with regard to this question; "In a number of cases the roentgen ray (examination) of the lungs was negative, and after amputation, radiation of the chest was performed on one or more occasions; in spite of which metastasis developed. Similar observations in three cases of sarcoma of the soft parts. Up to the present time I have no evidence that radiation of metastasis of the lungs has had any effect even if done before metastasis shows in the roentgen ray." From this statement we are forced to accept one of the three following conclusions: (1) the dosage was inadequate, (2) the quality of the radiation was not suitable, or (3) radiation will not achieve the destruction of such metastatic foci. There is the further possibility that if radiation is to be really effective in controlling metastatic dissemination to the lungs not only the mediastinum should be treated but also the lungs, because metastatic emboli must often be carried beyond the larger radicles well into the substance of the organ.

If an attempt is made to administer so-called prophylactic treatment to the contents of the thoracic cavity for metastatic sarcoma or carcinoma, such treatment should be extremely thorough and should be given early, even though it be impossible to demonstrate metastatic foci.

Unfortunately, in the majority of cases when the liver or lungs become demonstrably involved, the condition is usually almost hopeless. We may, however, look forward to the time when further developments in technic may make it possible to do more toward checking metastatic deposits. Pfahler has shown that in some cases it is pos-

sible to influence the development of metastasis in the bony substance of the vertebral segments. However, we are not justified in increasing the discomfort and suffering of a dying fellow-being when we know that all our previous efforts to cure him have been unsuccessful.

The group of malignant conditions classified under the general head of lymphoblastoma, which includes Hodgkin's disease, lymphosarcoma, and allied conditions, present a difficult problem. Characterized as they are by a tendency to progressive involvement of the lymphatic elements their exact status remains unsettled. In many cases in which the cervical glands are enormously enlarged, we can obtain a rapid and at times a truly startling reduction by means of radium. Other important groups of glands, such as the mediastinal and paravertebral, should also be treated, and this can be done most efficaciously by roentgen rays. It is questionable if the reduction of enormous adenopathies by radium may not in some cases be too rapid, and if a more gradual, though slower, regression would not yield better results. For the present we must be guided by our judgment in individual cases.

Preoperative radiation.—The practice of radiating a region after preliminary surgical amputation of the grossly malignant tissue has become a routine practice in many cases, as in carcinoma of the breast. Although a sound technic may yield good results, it is doubtful if our hopes are really justified or will be realized. Often operation performed with the intent to rid the patient of cancer leads to more or less rapid dissemination by grafting, or by venous or lymphatic absorption. The rational procedure, therefore, would seem to be for the surgeon not to operate before the involved part and its lymphatic drainage have been thoroughly radiated. Aside from the principle involved this would be of decided advantage in cases of carcinoma of the breast particularly, because the radiation could be administered much more effectively before operation, since there would not be a recent wound to prevent the arm from being well abducted. The entire axilla could thus be much more thoroughly and uniformly treated, and the tendency to malignant cell dissemination at the time of operation would be diminished. This principle may be applied to the surgical treatment of malignant conditions in general, except, of course, in the cases in which surgery is intended as a preliminary step before radiation. The surgeon wishes to know how long an interval should be allowed between radiation and operation. The early response of tissues subjected to radiation consists essentially in a modified inflammatory reaction, begin-

ning as usual with edema; the reaction is more intense and more localized if radium is used, and less intense and more diffuse if roentgen rays are used. The tissue cells gradually recover if the dose has been light; there is inhibition of their reproduction and development if the dose has been moderate; the cells are completely destroyed if the dose has been lethal. The products of such destruction are removed by autolysis and absorption, and later are replaced by fibrosis. This principle applies to normal as well as to pathologic cells. Generally neoplastic cells are more sensitive to radiation than normal tissue cells, and on this fact is based the entire radiation treatment of malignancy.

In many patients radiation produces so-called deep radiation sickness, a temporary state characterized by nausea with or without vomiting which may be quite pronounced, anorexia, headache, a sensation of general weakness, nervousness, and sometimes by fever. This state may last in some degree for from a few hours to several days; a few patients remain nauseated and weak for as long as two weeks, during which time they eat little and lose weight. Such reaction, which is usually shorter and much less severe in persons treated with radium than in those treated with roentgen rays should be allowed to subside completely before the patient is subjected to the ordeal of a major operation. As a rule, severe reactions are observed only when some part of the abdomen has been treated, and this is particularly true of the upper half. Therefore, the interval between radiation and operation must depend largely on the relative importance of these factors in a given case. In carcinoma of the breast radiation sickness is usually either absent or slight and so the operation could readily follow within a week. In carcinoma of the uterus, however, the radiation is administered by means of radium internally and by external roentgenization, and the interval should be from three to four weeks.

After radiation the tissues should be in comparatively good condition for operation and the surgeon should not encounter any particular delay in the repair of the wound. It is doubtful if after a single course of treatment the surgeon will have any difficulties in carrying out the various steps of the operation, especially if a proper interval has been allowed before operation. Even though the operation is made more difficult by radiation, few surgeons would hesitate to adopt it if the final results from the standpoint of the patient can be improved. Pre-operative radiation should also tend to minimize the danger of tampering with a malignant lesion in order to obtain a specimen for diagnosis.

Postoperative radiation.—Such postoperative treatment often may be more or less illusory. The most important requirements in rendering innocuous such invisible malignant elements as may have remained after surgical ablation is a correct selection of the agent and its use in adequate dosage. Should radium or roentgen rays be used? If we wish to sterilize an entire region, as following removal of the breast, radiation should be administered not only to the field of operation, but to its lymphatic drainage. Roentgen rays properly applied will best meet the condition. Radium should be reserved for small well defined territories, especially if the agent can be introduced into the center or the substance of the tissues, as the vaginal vault following hysterectomy (in conjunction with roentgen rays from the outside), or into the cavity left after the removal of a tumor of limited size. However, the radium should preferably be introduced at the time of and as a part of the operation. Radium used postoperatively, and blindly pushed or slipped into a drainage tube placed by the surgeon at the time of the operation is, at best, a very uncertain procedure.

If there has been no preoperative radiation, the patient should receive the treatment as soon as possible after operation. If the operation has been preceded by radiation the postoperative interval must be governed by the preoperative interval; due consideration should always be given to the patient himself and not merely to the pathologic factors of his condition. In general, from one to two weeks should be allowed between operation and radiation. In cases of carcinoma of the breast treatment might be commenced after one week, whereas it might seriously jeopardize the patient's chances of recovery if radiation were begun so soon after an abdominal operation.

How often should this postoperative, or so-called prophylactic radiation, be repeated? In the absence of glandular involvement, if the dosage has been estimated correctly, two to three thorough courses of treatment should be sufficient, particularly if one of these courses has been administered before operation. If the dosage has not been correctly estimated, however, we can hardly expect to achieve good results by prolonging our efforts indefinitely.

RECENT DEVELOPMENTS IN TECHNIC

During the past few years radiologists and members of the medical profession in general have been startled out of their usual complacency by reports of wonderful advances in the roentgen-ray therapy of malign-

nant diseases. Such reports have emanated very largely from German clinics and have led us to believe that very much better results can be obtained than formerly.

A study of original sources and the reports of several American observers in Germany show that no two of those clinics employ the same technic. Although there is a wide difference of opinion with regard to many details in the application of treatment, there is a reasonable degree of unanimity on a few points; (1) the use of higher voltage; (2) the use of "higher" filtration and the advantages of copper or zinc over aluminium as a filter, and (3) the use of increased focal distance. There are strong theoretical reasons for believing that these factors will exert a great influence on pathologic processes of a neoplastic nature, but only time and greater experience will enable us to decide whether or not such influence will be purely beneficial and to what extent.

Seitz and Wintz have advanced the idea, based on what seems to be very painstaking research, that different malignant and other conditions respond to definite dosages. Thus, they have found that the dose for carcinoma lies between 100 and 110 per cent of the unit skin dose; the dose for sarcoma is given as from 65 to 70 per cent, and the dose for castration was determined to be 35 per cent. These figures, I believe, were not intended to be interpreted too literally. It would be very difficult indeed to reconcile any such fixed limits of dosage with what we know of the very considerable variability in the metabolism of a given type of malignant cells. For example, in carcinoma there is often a tremendous difference in activity between tumors in patients of the same age, not to mention the variable activity of tumors in patients of different ages. Even the influence on the growth of tumors of such factors as lymphocytic infiltration, fibrosis, differentiation, and hyalinization, either singly or in combination,³ make it very difficult to accept such arbitrary ideas of dosage.

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RELATION OF UROLOGY TO GROUP MEDICINE*

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The modern tendency of the practice of medicine to become divided into different specialties is a natural process. With the accumulation of data resulting from countless sources of progress and research it has become impossible for one person to possess a thorough knowledge of all the various branches of medical practice. The creation of special fields has afforded opportunity for a concentration of interest and research, and has resulted in rapid progress in the diagnosis and treatment of diseases in practically every field.

Although the advantages of specialism were first recognized by the medical profession, its efficiency was soon recognized by the general public. As a result, many patients consulted specialists primarily for their various ills, ingoring the general practitioner, except possibly for acute or trivial conditions. The general practitioner rapidly lost caste and the specialist was put in a position of unnatural prominence. It was gradually realized, however, that general medicine is, after all, the root and trunk of the practice of medicine, and that specialization is only a branch. This realization of the situation was accentuated by the errors resulting from the artificial isolation of the various specialties and by economic factors. In the endeavor to find the most efficient, practical, and economic relationship between general medicine and specialization, and to meet the necessity for coöperation, group medicine developed.

Group medicine at present seems to be the best solution of the problem. By such an arrangement the various specialties become properly adjusted to each other and to general medicine; in fact, in this way can they best perform their natural functions. The principle involved is being tested in several forms, and it remains to be seen which, by survival, will prove to be the fittest. Minor details, such as the control of the organization and financial arrangements, will be adjusted to suit the environment and personnel of the group. Doubtless several

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forms will remain which will be best adapted to the various circumstances. Thus, rural communities will probably demand a different formation of the group than that required by larger communities. To what extent state paternalism will guide such groups is another question to be solved. A loose system of coöperation between the various specialties represented has been established, to their mutual advantage, in several large hospitals. This method, however, lacks the harmony of interest and the smooth coöperation which exists in more closely associated clinical groups.

Since I have had the opportunity to observe the practical application of group medicine for a number of years, it occurred to me that a short review of the principles involved would be of interest in their application to one of the special branches of medicine, namely, urology.

According to the system established at the Mayo Clinic practically all patients are first examined by general diagnosticians. After a complete general examination the symptoms determine which of the various special consultants should be called. For example, the clinical data, other than those frankly suggestive of involvement of the urinary tract, which indicate consultation by a urologist, are as follows: (1) history of previous hematuria or pyuria, even though urinalysis is negative for the time being; (2) pus or blood cells in the urine, even though no other symptoms or physical data are suggestive of involvement of the urinary tract; (3) any tumor in the upper lateral abdomen or suprapubic area; (4) a roentgenographic shadow suggestive of location in the urinary tract; and (5) a history of abdominal pain without definite evidence of disease in the intra-abdominal organs.

Records in the Mayo Clinic show that during 1920 cystoscopic examinations were made on 5860 patients. During the same period 60,000 patients were registered at the Clinic. It is thus evident that approximately one of every ten patients who registered submitted to cystoscopic examination. Twenty thousand patients submitted to operation, and of these 1,030 (5 per cent) were operated on for lesions of the urinary tract. One hundred fifty (16 per cent) of the 1,000 were also operated on for other lesions; the majority had had diagnoses of lesions other than those of the urinary tract. The completed diagnosis for patients with multiple lesions varied from one to five lesions in various parts of the body. This is convincing evidence that to secure complete diagnosis as well as treatment the close coöperation of the general diagnostician and the various other specialists is necessary.

The question is often asked: "How does it happen that such a relatively large number of patients with lesions in the urinary tract are operated on at the Mayo Clinic?" In a similar number of patients in general practice the proportion of patients in whom such lesions are recognized would be much smaller. The explanation lies partly in the fact that a large proportion of the patients in whom lesions of the urinary tract are diagnosed have no typical symptoms of such lesions. The number of patients suffering from disease involving the urinary tract who have correct diagnoses prior to their arrival at the Clinic is surprisingly small, in spite of the fact that many of them have been examined by fairly competent general practitioners. Not alone does the exact location or identity of the disease remain unrecognized, but in many instances the existence of any disease in the urinary tract is unsuspected. It is very evident that many of these patients would never have been brought to the attention of the urologist who is not associated with other physicians in his practice. The majority of such urologists usually have patients referred to them for examination because of pronounced urinary symptoms, such as frequency, difficulty, or hematuria. As a result many patients with lesions in the urinary tract without such symptoms do not have the benefit of skilled urologic investigation, and the condition is either first recognized in the advanced stages, or on surgical exploration, or it is not recognized at all.

COMMON PROBLEMS ARISING IN THE CLOSE RELATIONSHIP OF UROLOGY TO THE DIFFERENT SPECIALTIES

Probably the most closely related of the specialties to urology is roentgenology, and it is difficult to imagine how either specialty could attain any degree of accuracy without mutual coöperation. A certain number of shadows appear in roentgenograms of the urinary tract which may be correctly interpreted without further data; they are, however, comparatively few. It is quite impossible, in spite of technical accuracy or long experience definitely to determine from the characteristics of a given shadow whether or not it is in the urinary tract. The conscientious roentgenographer describes the majority of such shadows as either suggestive of stone, questionable, or negative, and reserves a positive diagnosis for comparatively few shadows. The clinical history will be of value in the interpretation of shadows, but far greater accuracy will be attained from the data derived from cystoscopy, ureteral catheterization, and the urogram. Not only are such data necessary to the

accurate interpretation of the shadow in the roentgenogram but also they are often of considerable practical value in its exact localization. In fact, the data obtained from urology and roentgenology are so interdependent for accuracy that the separation of the departments in different offices or different buildings is highly impractical.

The data offered the internist and the surgeon by the urologist in the differential diagnosis of abdominal lesions are often of great value. In fact, a course of training in urology sufficient to enable the modern internist to become familiar with the clinical symptoms of diseases of the urinary tract would be most valuable. From the standpoint of the internist the conditions which are most frequently the source of confusion are lesions with radiation of pain to the renal or suprapubic area; abdominal tumors, particularly those situated in the upper lateral quadrant; coincident lesions occurring in other organs together with the presence of pathologic elements in the urine; abdominal lesions with a history of previous urinary symptoms, and doubtful sources of continuous increase of temperature. To the clinician the differential data afforded by the urologist are often of great value, if only by excluding the kidney from possible involvement. In the course of differential diagnoses involving the urinary tract it must be expected that a large number will be negative, but it must be remembered that negative urologic data are often fully as valuable as positive data. From the urologist's standpoint, the coöperation of the internist is necessary if the primary disease is in the urinary tract, and if there are symptoms suggestive of coincident disease in the alimentary, circulatory, or thoracic tracts.

Tumors in the upper lateral abdominal quadrant, without localizing clinical data, often baffle the internist in his attempt to identify them. The data obtained by abdominal palpation are usually insufficient accurately to distinguish the tumor involving the kidneys from the tumor of the surrounding organs. Experience, when checked up at the operating table, will usually lead the clinician to scepticism with regard to his power of differentiation by means of palpation.

Since the radiation of the pain caused by lesions in the perirenal organs and pelvic organs may be closely simulated by the pain caused by lesions in the urinary tract, the subjective symptoms are necessarily often insufficient. The greatest confusion arises in cases of hepatic and appendiceal lesions, with radiation of pain into the renal area, because of the fact that with lesions in the intraperitoneal organs

the radiation and localization of pain is often posteriorly, whereas with retroperitoneal lesions the radiation may be reversed. Another source of confusion arises from the existence of a definite intra-abdominal lesion and evidence of coincident disease in the urinary tract. It may be more than a matter of coincidence that infections of the gallbladder are often accompanied by a slight degree of urinary infection. Complete urologic data are, of course, necessary in order to ascertain the source of any pathologic elements in the urine.

A definite group of patients are observed whose only evidence of disease is a persistent fever, and they may be a source of anxiety to the internist who endeavors to find the cause. The urologic data may be of value, particularly when there is a previous history of indefinite urinary symptoms and when even a few pus cells are found in the urine. The possibility of an occluded renal lesion, a dormant pyelonephritis, a concealed infection of the seminal vesicle, a cicatricial renal tuberculosis, and so forth, must all be considered as possible sources of such fever.

In the past few years the desirability of cooperation between the specialties, neurology and urology, has been emphasized. In a discussion in the Section on Urology, of the American Medical Association several years ago, I called attention to the advisability of such close cooperation, and emphasized the fact that occasionally early lesions of the central nervous system can be recognized through cystoscopic data. Scarcely a day goes by that the Section on Neurology of the Mayo Clinic does not refer patients to the Section on Urology for cystoscopic data. The cystoscopic data concerning patients with early lesions of the central nervous system involving the posterior tracts of the cord have been made familiar in recent years by Caulk and others. On the other hand, patients with urinary difficulty or residual urine, who have no clinical evidence of urinary obstruction on physical or cystoscopic examination, should be referred to the neurologist for the exclusion of lesions of the central nervous system.

The orthopedist often requires the identification of pain or evidence of infection in the sacral or lumbar areas. Clinical differentiation of a psoas abscess and a sinus leading from a pyonephrosis may occasionally be difficult. Cystoscopic demonstration of a normal kidney or a pyonephrosis on the affected side will assist materially in ascertaining the source. Osseous and arthritic tuberculosis coincident with renal tuberculosis are not infrequent, and close cooperation between the urologist and orthopedic surgeon is essential to correct treatment.

It is very evident that occluded or dormant renal tuberculosis will not permit a good result following an Albee operation, or fixation of a tuberculous knee. The possibility, in cases of arthritis, of a focus of infection in the seminal vesicles or prostate must always be considered. The orthopedist has learned to realize that the presence of pus in the urine necessitates a careful search for its cause, even though urinary symptoms may be absent.

As a result of extensive investigation of pyelonephritis in infancy, the pediatricist has learned to realize the importance of even a few pus cells in the urine of children with obscure symptoms or fever. In the identification of the source of abdominal pain and hematuria, roentgenographic shadows, and microscopic pus and blood in the urine, the pediatricist is in much the same position as the internist in demanding the differential data afforded by the urologist.

In recent years the importance of foci of infection in the mouth, nose, and throat, and their bearing on infections of the urinary tract has been emphasized. No examination of a patient suffering from an infection of the urinary tract will be complete without excluding the possibility of the tonsils, teeth, and sinuses as foci of infection. On the other hand, an otolaryngologist will not submit a patient to operation if, on preliminary examination, any evidence of disease involving the urinary tract is found, without consultation with a urologist.

The relationship of diseases of the pelvic organs in the female to the urinary tract demands the close coöperation of the gynecologist and the urologist. The recent encroachment on the field of the urologist by the gynecologist has no logical basis. The distinction between urology of the male and of the female is highly artificial and will hardly be recognized in the future. On the other hand, the urologist is partly to be blamed since in the past for various reasons he has confined most of his attention to the urinary tract of the male. With the extension of his field and the broadening of his scope, treatment and diagnosis of lesions in the urinary tract of the female are coming more frequently under his observation. One of the advantages of the association of the urologist with group medicine is the fact that distinctions of sex are not recognized among the patients.

Often patients are examined whose disease is primarily in the urinary tract, and whose symptoms may be largely suggestive of disease in other organs, as was recently described by Bugbee. Not rarely with polycystic kidneys, particularly in the advanced stage, the only symptoms

are those referable to the alimentary tract, such as vomiting, anorexia, and gastralgia. The patient often presents himself to the internist because of "stomach trouble." Laboratory and clinical tests made of the renal function may show that these symptoms are due to renal insufficiency, and examination of the alimentary tract may prove it to be quite negative. Physical examination then discloses evidence of bilateral enlargement of the kidneys and the question of the advisability of surgical treatment arises. Similar clinical experience may be observed in cases of advanced pyelonephritis and bilateral nephrolithiasis, in which the renal infection has destroyed the renal tissue to such an extent that its function is greatly reduced. With renal insufficiency due to any of the causes named symptoms may also be suggestive of cardiac lesions, such as dyspnea or edema in the extremities. In cases of hydronephrosis the subjective symptoms are rarely referred to the urinary tract, and if the hydronephrosis is on the right side the appendix is practically always sacrificed before the renal lesion is discovered.

It is true that in many cases patients are referred to the urologist for further treatment as soon as involvement of the urinary tract is recognized, but with the present methods of practice I fear it is not always the case. All too frequently patients are observed who are either suffering with advanced lesions in the urinary tract where no attempt has been made to establish a diagnosis, or they have had the misfortune to be explored in vain, or incorrectly operated on.

A most important advantage offered by group medicine is in the increased facilities for graduate instruction in the various specialties. Such advantages are shared by both instructor and apprentice. The increase in clinical material and facilities should prove to be of considerable value to the urologist. The facilities for graduate instruction in urology, while thorough enough in a few large hospitals, have been too limited, and as a result there are a number of poorly prepared, self-styled urologists who possess but few of the qualifications necessary successfully to practice this complex and difficult specialty. With the formation of clinical groups composed of able and scientific men this situation should be greatly improved. There is no reason why such groups when composed of the right stamp of men, having proper facilities, both hospital and clinical, and financial endowments sufficient to insure permanency, should not become affiliated with departments of medicine of the graduate college in any university. This would insure academic recognition and control of graduate work in urology leading to a degree of Master

of Science or Doctor of Philosophy in Urology. Such association has existed at the University of Minnesota for several years and has proved to be a practical and desirable arrangement. The day is not far distant when similar working arrangements will exist in many other universities.

It may be argued that the independent urologist surrounded by the various specialists in his office building can easily obtain the consultation that may be necessary. Because of economic reasons alone such consultation will necessarily be limited to cases in which it is apparently absolutely necessary. As a result many lesions will escape observation and the clinical diagnosis is necessarily incomplete. Furthermore, through close association with the various specialties, as in a group, a common system of interpretation is developed which is very conducive to accuracy of diagnosis. The association of a competent urologist with other competent specialists with increased facilities for scientific observation and research is necessarily stimulating to accuracy and scientific progress. With the close association of the various fields of medicine the interest and the vision of every specialist are necessarily broadened. The advantages to the patient of such association are obvious, and as a result in the majority of instances he can expect (1) a more complete diagnosis, (2) economy in time and expense, and (3) better results.

It might be inferred that the association of the urologist with a group might submerge his standing and that he would become a small factor in the organization. The supposition has no logical basis since the importance of the urologist to the group depends largely on his own efforts. The field of urology if properly developed should become of major importance to the success of a clinical organization. There is no field which can be considered of greater importance in the aid of differential diagnosis than urology. Its financial returns are also worthy of consideration. With regard to personal remuneration: there is no reason why there should be any distinction made between the urologist and any other clinical or surgical field. Whether the urologist should also take care of the surgical treatment in his field is a question for argument, and I believe not of fundamental importance. I am frank to confess, however, that I believe there are many reasons in favor of the urologist's taking care of his own surgery. Whatever our feelings may be, from present indications, the association of urology in some form of group medicine seems inevitable. It would seem advisable that the

farseeing urologist consider such opportunities carefully and with a mind open to its many advantages.

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DISPERSION OF BULLET ENERGY IN RELATION TO WOUND EFFECTS*

LOUIS B. WILSON

The bizarre effects of missiles on tissues are very puzzling. The surgeon sometimes sees a great, jagged, torn wound of entrance made by a shell fragment which has penetrated only a short distance in the tissues yet causing injury at only an imperceptible distance from those parts actually touched in its course. On the other hand, he may see a wound caused by a small shell fragment or a grenade splinter, the point of entrance of which is so minute as to be almost imperceptible, and yet which interiorly has pulped tissue at a distance of more than 1 cm. from those portions actually touched in passage. Usually such shell or grenade fragments, deformed bullets, or other irregular missiles not only vary so much in their shape, but also in their velocities, neither of which can be accurately known beforehand, that it is practically impossible to discover by their study the laws by which their energy has been dispersed or to predicate the type and extent of tissue injury which may result therefrom. We must, therefore, confine our studies of principles to missiles of regular form and of at least approximately known velocities.

The chief interest centers around missiles of high velocity. Comparatively speaking, it is not the push of the elephant's shoulder with which we are concerned, but rather the kick of the mule. Though the former may be the more ponderable force, the latter creates the more disastrous results. Our experience with high velocity missiles is almost all within the last fifty years. The spears and arrows of savage peoples and of European armies of the middle ages produced their fatal effects most frequently by hemorrhage, since their velocities and their total energies were small and delivered through cutting edges. The projectiles of early firearms were planned from empirical experience gained in throwing stones from catapults and blunt pointed bolts from cross-

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bows. They were relatively heavy missiles of relatively low velocities and depended more on surface shock than penetration for their fatal effects. For more than a hundred years after the invention of the rifled gun barrel, large spherical lead bullets were propelled through it at very low velocities. The only gain from rifling was increased accuracy which lasted so long as the interior of the rifle barrel was clean and fairly free from eroded lead. It was not until there was developed in the American colonies, some time about 1725, a simple means for keeping the rifle barrel clean, preventing leading and checking the escape of gas at the bottoms of the rifle grooves that it became feasible to put enough powder behind a relatively small missile to propel it with sufficient velocity to give fatal wounds in large animals. This simple but effective device was the greased patch which was made, usually, of thin cotton cloth, buckskin or pig's bladder, and used behind a bullet of slightly less diameter than the caliber of the rifle. At this one stroke the colonial backwoodsman worked a revolution in firearms. He dispensed with the heavy iron ramrod and mallet previously necessary for driving home the oversized lead bullet. He swept the residue of powder out of the future track of the bullet every time he loaded his gun. He absolutely prevented leading of the barrel. He made a perfect gas check, thus permitting the use of all the energy of his explosive. He made it possible to use charges of powder of a size hitherto undreamed of. He increased velocities from about 500 f.s. to 1,600 or even 2,000 f.s. He thus flattened the trajectory of his missile so that errors of aim were minimized. He rotated his undeformed spherical bullet with great regularity, thus insuring high accuracy. According to a well-known law of physics, when he increased the velocity three times he increased the striking energy nine times with bullets of the same mass. This high velocity missile from the backwoods sharpshooter's rifle, though used by relatively few men, was a very potent factor in the winning of the colonials' war for independence. Unfortunately, records of wound production by it are largely a matter of tradition. In the hands of a few careful shots it continued to be a great tamer of the wilderness until our Civil War brought out as never before the importance of increased speed of fire, resulting in the development of the metallic cartridge. But black powder metallic cartridges did not readily permit the use of patched bullets. Thus, the powder residues eroded and the lead again fouled the barrels to such an extent that heavy charges with small calibers and resulting high velocities were not possible.

With the substitution in cartridges, first of paper patches around lead bullets, a system still used by Switzerland, and later with the discovery of smokeless power, the introduction of nickel, low-carbon steel or bronze jacketed bullets, the rifle tube could again be kept free of lead and of powder residue. Calibers could be reduced and velocities again increased to about 2,000 f.s. This was the approximate muzzle velocity of the missiles from the Mauser and Krag rifles of the South African and Spanish-American wars.

The earliest experiments in this important field were developed to practical use about 1870, and in 1875 Kocher, of Berne, then a young man, published the first series of experiments on wound injuries from high velocity projectiles. It should be noted, however, that the velocities with which Kocher experimented, from 1,800 to 2,000 f.s., while a very great increase over those of previous European and American cartridge type of military weapons whose velocities were from 1,200 to 1,400 f.s., were little if any greater than those velocities of missiles from the backwoodsman's rifle of the Revolutionary War period. I have, however, found no experiments other than incidental observations, chiefly concerning the effects on game, of the missiles of the Revolutionary War period. I think, therefore, that Kocher may properly be credited as the pioneer in accurate observations on wound effects of high velocity bullets. Following Kocher, several German, Austrian, French, and Roumanian observers conducted more or less extensive experiments on the effects of small caliber high velocity projectiles. In England most accurate observations were made by Sir Victor Horsley about 1895. In this country, Colonel Louis A. Lagarde was one of the earliest, most careful, and most thorough of experimentalists. Woodruff and Beyer have also conducted most careful and valuable experiments in this country on the ballistics of wound production.

Most of the observations of the experimenters already mentioned were conducted on bodies of men and animals. Some firing was done into cans containing water, wet clay, sand, marbles, etc. Much of the early attention was given to effects on bone. Of the work of the early experimentalists, that of Sir Victor Horsley and of Woodruff was most concerned with the problem from the standpoint of physics. Horsley attempted to discover the laws of dispersion of energy by firing directly into masses of clay and studying later in the dried mass the track of the missile and the disturbance of the mass in immediate relation thereto.

These studies, though made on missiles with relatively much lower velocities than those of military rifles of today, namely, approximately 2,000 f.s., while those of today are from 2,500 to 3,000 f.s., are very germane to our study of the effects of the most modern missiles since at long ranges the highest velocity missile falls to velocities of those of the older type. It must be constantly borne in mind, however, that the so-called "explosive effects" so rarely seen during the Spanish-American War were produced by missiles of the 2,000 f.s. type only at relatively short ranges and were therefore of much rarer occurrence than during the present war. It is the possible explanation of some of these puzzling explosive effects to which I wish to direct attention.

In 1914, 1915, and 1916, the medical and popular press of the various warring European nations conducted a most violent controversy, those of each country charging their enemies with the use of dumdum or explosive bullets. As everyone now knows, very few purposely deformable, and fewer still truly explosive, bullets were used by any of the European nations. The British, more properly to balance their bullet and make it conform more accurately in its ballistic coefficient to their tracer and armor-piercing bullets, did substitute for the forward end of the lead core a mass, first, of aluminum and later of hardened wood fiber, but these, in both instances, were covered with cupro nickel jackets with high tensile strength and did not deform more rapidly than the standard bullet of all-lead core. Occasionally hunting bullets with soft lead points were probably used in military weapons by individual soldiers on both sides. I have seen a few cartridges of German, Austrian, and French models loaded with these bullets. I have one odd-size American cartridge loaded with an expanding soft nose bullet recovered during the Chateau-Thierry advance of July, 1918. It, however, was taken from the body of a German sharpshooter who was using a German rifle adapted to the American cartridge which had been sent to Germany for experimental purposes in considerable quantities about 1912. A careful search of salvage dumps, both before and after the armistice, in both eastern and western France, resulted in the finding of thousands of cartridges loaded with what were commonly thought to be explosive bullets, but all of which on dissection were found to be either incendiary, tracer, armor piercing, or ordinary lead cored missiles. Of the thousands selected out of millions thus examined only one single cartridge containing an explosive bullet came into my possession. That was a cartridge found in a German ammunition dump in the Argonne after the

Armistice. It was adapted to the Austrian straight-pull Mannlicher rifle. It will thus be seen that we must look for the cause of explosive effects not in dum dum, soft point, or explosive bullets, but in the explosive energies of ordinary bullets either when undeformed and flying true or when deformed or flying erratically.

What are the principal "explosive effects" produced in tissues by undeformed high velocity rifle bullets flying head on? They may all be grouped for convenience of study into comminution of bone, the "blasting out" of soft tissue at the point of exit, the pulping of soft tissues around the track of the missile and injuries to distant parts by energy transmitted through fluid. The first two of these were thoroughly investigated by the earlier observers, particularly by Lagarde, Woodruff and Beyer in this country, by Kocher in Switzerland, by Delorme and Chevasse in France, and by several Germans. So far as the variations in explosive effects on bones are concerned, I need to call attention to but two phenomena which together will explain the principal factors involved. If you press hard enough and slowly enough with your fist against the center of a window pane, you will crack the glass over its entire area before making a hole in the glass. If you fire a high velocity bullet through the center of a similar pane of glass, you will make a hole not many times the diameter of the bullet and with few, if any, cracks radiating therefrom. The outer portions of the glass will remain intact. The low velocity of the pressure in the first instance permits the energy to be transmitted throughout the entire area of the glass before the pressure ceases. The high velocity in the second instance relieves pressure before the energy has had time to be transmitted to distant areas. In the center of shafts of long bones this variation in energy release is the principal factor in the variation in fracture effects, providing, of course, the missile in each instance is flying head on.

If you fill a tomato can with small marbles and fire a high velocity rifle bullet through it you will find that some of the marbles will make dents in the can, but that the point of exit of the bullet will barely admit your little finger. If you fill a can with sand and fire a similar bullet through it you will be able to put two or three fingers in the hole of exit. If you fill the can with water and fire through it, the whole far side of the can may be torn out. Similarly in bones struck by missiles of the same velocity, portions of bone of high density show less local shattering than those of lower density, the shafts of long bones less than the head, and so forth.

The variation in the "blasting out" of soft tissues at the point of exit is a phenomenon which is explicable largely by a consideration of secondary missiles, that is, the placing in motion of fragmented tissues, particularly bone. We must, however, not think of fragmented bone as the only secondary missile. The missile effects of even water from a fire hose in quelling riots is a matter of common knowledge. One can readily understand then how even fragments of the softest of tissues to which high velocity is imparted by a rifle bullet may become serious missiles in blasting out the soft parts around the point of exit. There is no doubt that the conical form of these blasted out cavities is due to the direction in which the energy is transmitted. This is a resultant of several lines of force and depends upon the shape of the conical head of the bullet, and in some degree on the variation in the ratio between the energy of rotation and that of translation as the bullet is slowed in its passage through the tissue without at the same time being materially retarded in its revolutions.

One of the most difficult things for military surgeons to appreciate in the recent war was the pulping of soft tissues along the track of high velocity rifle bullets. Failure to appreciate this by any of the warring nations early in the war and by many American surgeons even as late as the summer of 1918 no doubt resulted in many instances in insufficient cleaning out of pulped and infected tissues with resulting gangrene and death. Our Cuban experience, owing to lower velocities and longer ranges, had not taught us the frequency of pulping effects with higher velocities and shorter ranges, and the experimental data were insufficient and unconvincing.

Most of the experiments had been either on the bodies of men or animals, or in such mediums as sand or clay, which do not readily lend themselves to an accurate determination of the distance to which the energy of high velocity missiles may be transmitted. In attempting to throw further light on the problem, I began a series of experiments in 1916 using gelatin of various known percentages as a medium into which to fire. These experiments were interrupted by call to active service in January, 1918, and though I have resumed them recently, my increased knowledge of wounds, gained during the war, has led me to see so many ramifications of the problems involved that I cannot look forward to the completion of the experiments in the near future. It may be of interest here, however, to report progress.

Gelatin was chosen because it is a translucent medium, the densities

of which can be accurately controlled. I have used densities of 5, 10, 15, and 20 per cent of commercial gelatin in water. The hot mass is poured into cardboard boxes about 8.75 by 11.25 cm. surface area, and about 5 cm. deep. After the gelatin is cooled, the masses are fired through at a standard range of 50 feet, using the regular charge in the Springfield rifle. Besides observing the shattering of the gelatin masses, various other means have been taken to measure variations in dispersion of energy. Powdered charcoal has been placed on the surface of the gelatin and the distance to which the particles were driven into the gelatin



FIG. 384.—Dispersion of powdered charcoal in 10 per cent gelatin by Springfield bullet at 50 foot range.



FIG. 385.—Dispersion of powdered charcoal in 5 per cent gelatin by Springfield bullet at 50 foot range. Note that the charcoal has been driven about four times as far from the track of the bullet as it is in the 10 per cent gelatin (Fig. 384).

along the track has been observed. A small area in the center of the mass has been filled with powdered charcoal, and the distance to which particles thereof were driven carefully measured (Figs. 384 and 385). Thin fibers of soft black darning cotton have been sewed back and forth from side to side halfway up from the bottom of the box, gelatin poured in, and after being allowed to cool, the threads cut at their ends. With these, not only a practical definite measure of dispersion of energy has been obtained, but also the drawing effects on the threads has been observed (Figs. 386 and 387). These latter simulate the evulsive effects

produced by high velocity missiles on fibers of connective tissue, the muscle bundles, nerve sheaths, and so forth. For the further study of this latter phenomenon a layer of very fragile black silk net, known by the trade name of "maline," has been embedded in the gelatin halfway up from the bottom of the boxes and fired through. The fragile threads of this net are not shattered, but are drawn out from the woven fabric.

Now, these gelatin masses which have varied in their densities in a simple ratio, namely, 5, 10, 15, and 20 per cent solutions, have also varied greatly, and not necessarily in parallel ratios in their surface



FIG. 386.—Dislocation of threads in 10 per cent gelatin by Springfield bullet at 50 foot range.



FIG. 387.—Dislocation of threads in 5 per cent gelatin by Springfield bullet at 50 foot range. Note that threads have been disturbed at least four times as far from the track of the bullet as they have been in the 10 per cent gelatin.

tension, their elasticity, and their viscosity. The variation ratio for each factor, however, has been uniform for that factor. Though this variation has no doubt been complicated, it has been extremely simple compared to the complex variations in density, elasticity, viscosity, and so forth, in the different anatomic structures of different men of different ages, different degrees of leanness or fatness, different degrees of contraction or relaxation of muscles and in different amounts of fluids in tissues, as well as in hollow organs. It is believed, however, that the general principles which may appear from the study of the distribution of missile

energy in such gelatin masses are applicable to those phenomena which are met with in wounds in living men.

Without wearying you with the mass of details, on many of which observations are still incomplete, I may sum up the results of the principal observations so far as they have gone by saying that, speaking generally, and without any pretense of high mathematical accuracy, my experiments seem to show that the energy of a high velocity missile passing through gelatin masses of different percentage densities is dispersed in an explosive degree to distances approximately inversely as to the square of the percentage densities. That is, explosive effects are produced in a 5 per cent gelatin approximately four times as far from the bullet's track as in a 10 per cent gelatin, nine times as far as in a 15 per cent gelatin, and sixteen times as far as in a 20 per cent gelatin. Now it is no doubt true that a wave set up in gelatin masses of any of these percentages proceeds completely to the periphery of the mass, but it is not true that the gelatin is fragmented to the periphery, or that particles of charcoal are driven to the periphery.

These experiments on gelatin masses have been supplemented by studies on the effects of similar missiles in living and dead animal tissues and by observations at the autopsy table on fatal war wounds. So far as one can estimate the relative densities of the tissues, the principles somewhat crudely worked out for gelatin seem to hold for cartilage, fibrous connective tissue, muscle masses, and soft glandular organs. It has been impossible by the methods so far adopted to measure the dispersion of energy in fluids. However, certain effects have been noted, which will be mentioned later, and further experiments are now in progress.

The practical lesson to be derived from these experiments for the military surgeon's use is that wounds made by rifle and machine gun bullets of high velocity show destruction of soft tissues, even when no bone has been struck, at distances very much farther from the track of the missile than one would be led to suppose from his study of the effects of missiles of low velocity such as the older military bullets or such as revolver bullets, wounds from which are usually encountered in civil practice. It must be remembered also that increase in energy from increased velocity follows a very definite physical law, the energy of missiles being proportional only directly as to their mass, but proportional directly as to the square of their velocity. Thus, a rifle bullet of 150 grains has only twice as much energy at the same velocity as a

pistol bullet of half the weight, but if moving at a velocity of 2,400 f.s., it has sixteen times as much energy as a pistol bullet of the same weight, moving at a velocity of 600 f.s. Furthermore, this energy would be

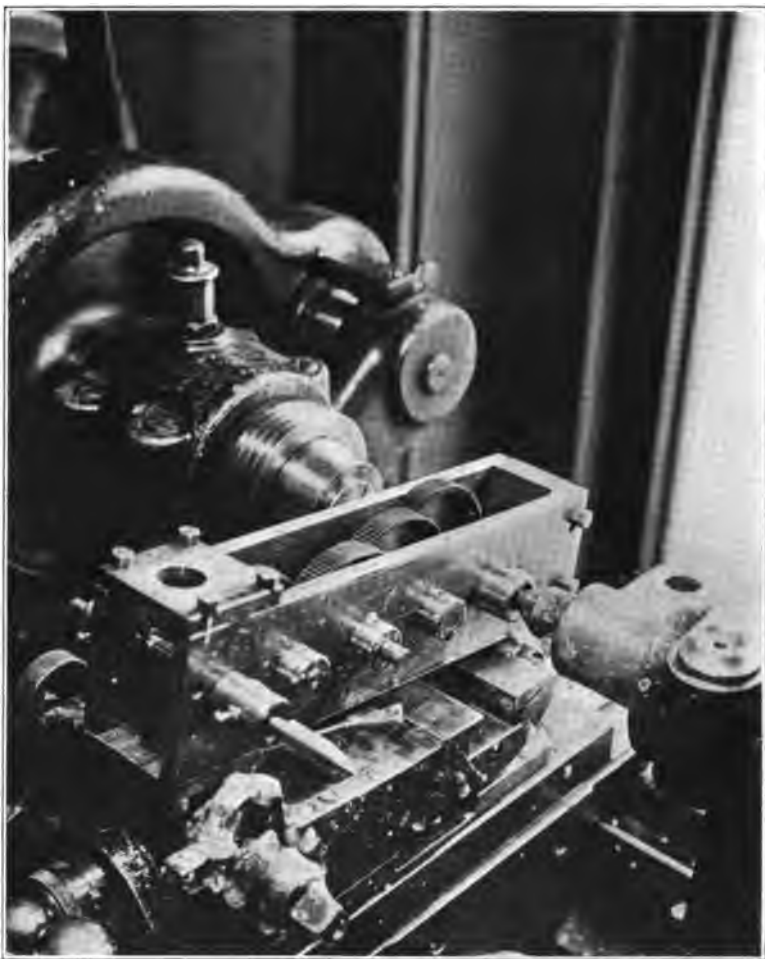


FIG. 388.—Lathe-driven machine for spinning Springfield bullet at approximately normal rotation speed for experiments concerning rotation energy effects in wound production. Photograph taken immediately after an experiment showing how gelatin is scattered about thereby.

dispersed sixteen times as far into the tissue as would the energy of the pistol bullet. Thus, while it may be perfectly safe in civil practice merely to clean out superficially the track of the relatively low velocity

32-caliber jacketed pistol bullet through soft tissues, if in military practice pulped dead tissue is left in the track of the very high velocity 31-caliber Mauser rifle bullet, serious results are certain to follow. This necessity for wide débridement was relearned by sometimes sad experience by the military surgeons of all nations in the recent war. It is hoped that it will never again be forgotten.

In addition to the pulping effects by transmission of energy laterally by a rapidly moving missile, the very great evulsive effects of the missile



FIG. 389.—Dislocation of threads in 10 per cent gelatin by instantaneous spin of Springfield bullet rotating at 178,000 r. p. m. in machine shown in Figure 388.



FIG. 390.—Dislocation of threads in 5 per cent gelatin by instantaneous spin of Springfield bullet rotating at 178,000 r. p. m. in machine shown in Figure 388. Note that threads are disturbed at least four times as far from the point of insertion of the bullet as in the 10 per cent gelatin (Fig. 389).

in ripping out fibers of connective tissue particularly from muscle aponeuroses and from the sheaths of vessels and nerves must not be lost sight of. This effect has been well illustrated in my gelatin experiments by the ripping out and tangling up of the enmeshed fibers of cotton and silk. That the rotary motion of the bullet may be a considerable factor in this effect is shown in Figures 389 and 390.

The second practical lesson to be learned by the military surgeon is that the softer the organ or tissue, the further away from the track of the missile will serious secondary results of injuries occur. The pulped

tissue not only is almost certain to become the nidus for the growth of pathogenic bacteria which had been disseminated through it on fragments of dirt and clothing carried into the wound by the missile, but certainly the pulped muscle and probably also other shredded organs break down quickly and give out toxic products which according to Cannon's experiments are one of the causes of so-called secondary traumatic shock.

Soft glandular organs, such as the kidney, spleen, and liver and the nerve trunks, which have not been even touched by high velocity bullets may be seriously affected by the transmission of energy to them through intervening soft parts. This is of great surgical importance. It is a bit unfortunate that Sir Anthony Bowlby's Bradshaw lecture, in 1915, in which he quoted the observations of Stokes and McNee to the effect that the liver and kidney, for example, may show extensive interstitial hemorrhage and disintegration of the parenchymal cells at considerable distance from the site of obvious injury, should have stimulated certain British pathologists to deny the presence of these so-called hydrodynamic effects because in their experiments they had failed to observe them. Had they taken into consideration the great variations produced by relatively slight variations in density of the perforated mass and in the velocity of the missiles they need not have been misled. It is only when these factors are accurately controlled that one gets comparable data.

But it is in the production of minute injuries to the intima of blood vessels that one meets with the most striking results of the transmission of energy in mediums of low density and viscosity. Sir George Makins says: "Of all the experiences in the present war that regarding the frequency of occurrence of contusions (to the blood vessels) and the significance of this form of injury in the causation of thrombosis, secondary hemorrhage and traumatic aneurysms, is perhaps the most novel." This was written by a surgeon with extensive South African war experience and at the end of the recent war despite the statements by several British observers, in 1916, describing the improbability of such injuries. My gelatin experiments seem to indicate that the transmission of explosive energy is more directly related to variations in viscosity than in density, that is, the less the viscosity, the farther energy is transmitted. Now, the viscosity of blood is very much less than that of 5 per cent gelatin. The distance to which energy of high velocity missiles is transmitted in 5 per cent gelatin is astonishing. How much more so,

then, must it be in blood of yet lower viscosity. Makins calculates these minute injuries to the blood vessels. He says, "The mischief may extend widely within the vessels from the spot where the external indications are the strongest," and points out the extreme importance of their relationship to thrombosis, secondary hemorrhage, and aneurysms. He does not, however, present an adequate explanation of the dispersion of energy in the blood which results in the distant injuries. While I am not prepared to make dogmatic statements in the face of the many hypotheses and lengthy discussions, particularly those of Teutonic observers, given in detail by Borst in the recently issued volume of Aschoff's "Pathologic anatomy," I am convinced from my own experiments that the phenomenon is closely related to the relatively low viscosity and density of the blood and that it may be explicable along the lines of those principles of physics fairly well worked out by Worthington in his "Study of splashes." The important thing for the military surgeon to bear in mind is that when a high velocity rifle bullet has passed through or even near an important blood vessel there are almost certain to be minute slit-like lesions in the intima, which may be scattered in areas far away from those parts actually touched by the bullet in its passage, and that these lesions in the intima, even if uninfected, may cause thrombosis, fatal secondary hemorrhage, or slowly developing aneurysms. The lesions also may become the focus for the growth of bacteria which have found their way into the blood. When a rifle bullet has passed completely through and out of the body or of a limb, thus indicating its relatively high velocity, and either through or in close proximity to an important blood vessel, and when at the same time the tissue is evidently pulped at considerable distance from the track of the missile, the only safe surgical procedure is ligation of the vessel at a relatively long distance from the track of the missile.

At some future time I hope to present further experimental data on high velocity missiles with suggestions as to their surgical significance.

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THE TRAINED NURSE*

CHARLES H. MAYO

We are all interested in the care of the sick which has been greatly changed from ancient customs. The modern methods, proved to be the best, are now accepted by the public. It is only a few decades since hospitals, some in truth hot-beds of infection, were looked on as places to die in, a place of refuge especially for the poor. They are now sought by the intelligent sick who desire the best possible care. No one factor has brought about this revolutionary change. The better knowledge of disease, its transmission and prevention by the educated public who now demand more of the physician, has probably been the greatest factor in bringing about the reorganization; the development of public education in hygiene will be the next great factor.

The trained nurse has given nursing the human, or shall we say, the divine touch, and made the hospital desirable for patients with serious ailments regardless of their home advantages. The rich patient who can pay the price, and the poor patient who can pay nothing may secure the highest service in sickness. But how about that larger group of patients in the great middle class who, neither rich nor poor, would be glad to preserve their self-respect by paying to the limit of their ability? The key-note of hospital efficiency today or of any other great movement depending on combined effort is organization. So few hospitals pay their expenses that, like educational institutions, unless they are supported from a bequest, they must be assisted by charity or by the city, state, or some religious or similar organization to make up the yearly deficit. Can a hospital give the minimum standard of care without the most efficient help? The answer is "no" as opposed to public service and the support of standards of efficiency. Yet, if the hospitals have competent physicians, surgeons, interns, superintendents, and trained chiefs of nurses with intelligent and willing undergraduates, training can be accomplished in a comparatively short time. The nursing

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and care of the sick is a matter of education, and ignorance may be overcome. Knowledge is acquired by a compelling force from within, by desire, or from without, by compulsion. No matter how efficient, in general, are the officers of the latest addition to the nursing staff, the hospital will not be safe and truly serve the best interests of the sick without supervision by some one in authority. This cannot be reversed; the most competent nursing staff cannot replace those who are responsible for the direction or the administration of the organization.

What can be done to maintain the efficiency and save the professional life and dignity of our nurses; can we help them to help themselves? They are compelled to study and labor diligently for three years after having achieved a high standard of general education. They are overtrained for nurses and undertrained for physicians. It is true that the training is good for them; the greater number marry, and the wide general knowledge they have acquired is, in fact, of more value to them, their children, and the communities in which they live, than are college degrees, as it contributes to better national health and a more practical citizenship. The records of St. Mary's Hospital in Rochester show that of the nurses graduating for the ten years preceding the last three years 1 per cent are dead, and 54 per cent are married. Of the class of four years ago, 31 per cent are married. If, then, excluding the last three year graduates, 2 per cent are out of the work, only 43 per cent are left in the service of the previous ten year period that has taken the nurses three years of hard, continuous study and work to learn, as long in actual time spent as it takes to study medicine and three to four times as long as it takes to acquire a degree as chiropractor. It is evident that the foundation requirements are too high for the average demand, and in all fairness must be made a little higher by specialization, and by giving added responsibilities in positions as technical assistants, or the period of training must be shorter in conformity with requirements for ordinary nursing duty in order that a greater number may obtain the benefit of this educational training.

The course of training should be two years with post-graduate study for the third year, which should be optional, and it should be possible to take it at any time desired, so that those who remain in the work may fit themselves for the work in which there is greater opportunity for service and securing personal distinction. Chief nurse in the hospital, chief surgical nurse, nurse in dressing service, anesthetist, county, city

and school nurse, industrial and child welfare nurse, dentist's aid, physician's aid, and laboratory technician, are but a few of the many positions waiting. It is far from my desire to destroy nursing standards; on the contrary, I wish to advance them for those who remain in the profession with a demand for recognition of ability, responsibility, and honor which will then be accorded.

The patient sends for the physician first. The physician secures a nurse if desired, or he sends the patient to the hospital, where a nurse in rotation is assigned by the superintendent. The physician or surgeon must assume the responsibility, even though death occurs from an accident in care.

Any labor union in which the candidate draws pay or receives only board and lodging while in training, as does the bricklayer, plumber, or carpenter, protects the job by limiting the number of apprentices. In professional life there is some danger in overorganization. The nurse, in accepting unionism, must carefully watch the policies of the organization that they be maintained along professional lines with their legislative efforts directed unselfishly to better care of the sick. As a physician I am proud that legislative acts sponsored by nurses, with the one exception of that sponsored by medical anesthetists, have always been in the interest of public health without thought of advantage to the profession. The physicians' services are always at command for charity, which service the nurse cannot give.

In the interests of the sick I strongly advocate a return to the two-year course as a minimum standard of nurses' training and the development of post-graduate work with a special diploma for advance training. In urging this, I wish to call attention to the fact that in the Great War the medical department under the surgeon-general was developed to the highest efficiency by the valuable aid of the leaders of the department of nurses in Washington, and in the service abroad and at home. Most of the leaders in this group were themselves two-year graduates, thoroughly capable and most devoted to their work.

It has been suggested that those who possess a high school certificate should be graduated in two years from a course in general nursing, and those desiring training in special branches continue or take such training at a later period. In some progressive cities, such as Minneapolis, the theory of nursing with the fundamental branches with six months of practical work in a convalescent hospital is now given as a vocational training course in the public school system.

IN THE TIME OF HENRY JACOB BIGELOW*

WILLIAM J. MAYO

To the members of the Boston Surgical Society, and to others in the audience who have grown up in the atmosphere created by Dr. Henry Jacob Bigelow, a man known to the older of you personally and to the younger of you by tradition, any attempt to portray new facts concerning his life and work would seem little short of presumptuous. But since Dr. Henry Jacob Bigelow was one of the great Americans whose work is of paramount importance and interest to the American medical profession, and since his achievements are a precious heritage of all Americans, it may be fitting at this time briefly to review certain data which without doubt greatly influenced the development of his career.

The Reverend Jacob Bigelow was the founder of the family in Massachusetts. Jacob Bigelow, M. D., LL.D., the second Bigelow, was born in 1787. He graduated from Harvard, taught in the Harvard Medical School, and later acquired renown as Rumford professor in the Department of Science, Literature and Art, of Harvard University. He was the author of many valuable papers on scientific subjects, and he held a high place in the American science of his day. Henry Jacob Bigelow, the son of Dr. Jacob Bigelow and the talented Mary Scollay Bigelow, was born March 11, 1818. He was graduated from Harvard in 1833. At that time there were ten professors at Harvard, including the president, and 230 students.

As a boy Henry evinced an extraordinary interest in mechanics. He was wonderfully skilled in the use of all kinds of mechanical implements, as well as in the art of making them. He was a leader in the younger social set of Boston. During his freshman year in college he organized and headed a student revolution. In reproving him for this serious offense his father said that he himself had committed such acts in his youth, and later repented of his folly. Henry replied that his reasons were quite the same; that he also wished to learn by actual experience the folly of his ways.

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After Henry had graduated from Harvard he began to study medicine with his father as preceptor, and from the first declared his intention of becoming a surgeon. He was house surgeon in the Massachusetts General Hospital from 1838 to 1839, and received his medical degree in 1841. At this time Dr. Oliver Wendell Holmes was teaching anatomy and physiology in the Medical School in Hanover, and young Dr. Bigelow went there to attend his lectures. Dr. Holmes was not only a literary genius, an anatomist, and a physiologist of the highest order, but was greatly interested in clinical medicine; he was the first to point out that puerperal fever was a form of surgical sepsis.

FRANCE, THE MEDICAL CENTER

In 1842, Dr. Bigelow went to Paris, at that time the medical center of the world. To children is given the power of readily acquiring languages; later, mathematics is acquired with the same readiness; but reasoning from cause to effect is a development of adolescence and early manhood. Critical observers believe that most men have unconsciously laid the foundation for future careers at a period of life well under thirty years. Dr. Bigelow went to Paris at the most impressionable period of his scientific life.

John Hunter, in the latter part of the eighteenth century (1728 to 1793), was the first to study pathologic anatomy as a whole. Before Hunter's time normal anatomy had reached a relatively high level of perfection by dissections on cadavers; but pathologic anatomy, while it had been highly developed in relation to certain organs or parts of the body, had by no means kept pace with progress in the study of normal anatomy. As the result of Hunter's work England became the center of the medical sciences, a position which she held well into the nineteenth century. One needs only to view the thirteen thousand pathologic specimens in the Hunterian Museum of the Royal College of Surgeons in England, put up, labeled, and numbered in black by Hunter's own hands, to realize just what this man accomplished in the development of medical science. He was aided only by the eye and by inferior types of microscopes.

Gerard Van Swieten, while not comparable with Hunter in any way, in about the same period (1700 to 1772), under Queen Maria Theresa, was laying the foundation in medicine and pathology in the great medical school in Vienna, a foundation which gave vitality to Vienna as a medical center for more than a hundred years.

The teachings of Hunter were eagerly seized by the French, who, with characteristic Latin ingenuity, at once began to study methods whereby practical use might be made of pathologic knowledge in the cure of disease. France quickly forged to the front in the development of surgical anatomy, technic, and operative surgery, and the leadership in medicine passed from England to France. The microscope had been greatly improved in France, thus making it possible to study in detail minute histology and pathology.

Dr. Bigelow was caught, at the most plastic period of his life, in the high tide of this flood of new knowledge. Was it any wonder that, with his creative genius for invention and mechanics, he should become so nearly French, and should flower under the guiding genius of the French people during this great period in the history of medicine?

Von Langenbeck, father of modern German surgery, was a student in France about the same time, and he carried to Germany the principles of applied art in surgery which the fundamental work of Hunter had made possible.

In 1847, Philadelphia was enriched by the coming of Mütter, who brought to America, from the great schools of Paris, a knowledge of orthopedic surgery.

Prof. David W. Cheever, who knew Dr. Bigelow well, thus evaluated the French influence on Bigelow's work:

As a surgeon, in method Bigelow was a pupil of the French school. To ingenuity he added dexterity, and to dexterity grace. He was alert, cool, practised; whenever he appeared on the operating arena it was as a central figure. Precise in touch, supple in movement, he added the polish of the finished artist to the nonchalance of the experienced operator.

Dr. Bigelow, however, did not become quite French. One is impressed with the fact that he journeyed from Paris to England, a most disagreeable trip, once a week to see James Paget. Paget was the great philosopher of surgical science of his day. He had a rare fund of knowledge gained from others, and he had great wisdom combined with intuition, and was able to correlate knowledge with experience. I remember well that when I was a schoolboy my father, in mapping out my future medical training, gave me Paget's book on surgical pathology. This book is one of the most fascinating I have ever read; and although I read it more than forty years ago, certain passages still stand out vividly in my mind. Paget's generalizations on pathology have never been excelled and seldom equaled. For example, in writing on

atrophy and hypertrophy, he says that continuous pressure produces atrophy, like bedsores, and intermittent pressure produces hypertrophy, like corns and callus. His description of the natural deterioration of age as the "calmness of decay" due either to a reduction in quantity, as in the withering of age, or to a reduction in quality, as in the obesity of age, is classic. Again, he speaks of the senile processes as age replacements of vital tissues by the introduction of earthly substances, atheroma, arteriosclerosis, and so forth, "as though man were becoming more earthly in preparation for the grave." The inspiration to Dr. Bigelow of seeing in Paget the Anglo-Saxon characteristics of soundness and sanity, with breadth of view, may be readily conjectured. Paget made generalizations that are as much a characteristic of the Anglo-Saxon mind as keen analyses and technical skill are characteristics of the Latin mind.

In Dr. Bigelow's training, therefore, the highest product of the French and English schools is exemplified. The form and method were from the French, but the principles were from Hunter and Paget, and the English school. As one reviews even sketchily the education of Bigelow, it seems difficult to improve or to equal it at the present time. Today the premedical student is overtaught. An attempt is made to give him a memory smattering of many facts. He is required to take cultural training of little value for his future work, such as higher mathematics more calculated for the training of an engineer than a physician. Two years of time at least are lost in premedical unimportant educational drill, too often under mediocre teachers and cloistered professors.

The Oriental races mature at an early age. They excel in memory tests and reach the height of mental growth well under forty years, with exceptions to prove the rule. They are brilliant medical students, but often poor practitioners. The Anglo-Saxon develops later, but he has a capacity for reasoning and for action based on reason, which does not falter with age. Where does history reveal the same number of men of other origin who were great men at seventy and eighty and even ninety years, with equal power of correlating and assimilating new facts?

Dr. Bigelow was not overtrained. He was allowed to think for himself in order that he might gain in wisdom that which he lacked in knowledge. Dr. Bigelow obtained his medical degree before he was twenty-five years. The average graduate in medicine today is over twenty-seven years, and if he takes a three-year fellowship he is over

thirty before he begins his work. An investigation of the graduates of medicine in the University of Michigan for a fifteen-year period showed that men graduating under twenty-five years were, on the average, more successful and worth more to their communities than those who graduated over the age of twenty-five.

While Dr. Bigelow was in Paris he had typhoid fever, and on recovering went to Italy to convalesce. He spent several months in Rome, and devoted himself to the art of drawing. The skill he acquired added greatly to his ability as a teacher later, in giving blackboard illustrations to the students.

DR. BIGELOW RETURNS TO BOSTON

Dr. Bigelow returned to Boston in 1844. At that time there were about 150,000 inhabitants in Boston, 162 of whom were physicians. Dr. Bigelow's ambition was boundless, and his self-confidence most remarkable. He did not hesitate to express his opinions in the presence of those high in authority, and chafed at attempts to control by authority of position rather than by ability.

Dr. Bigelow was a handsome man with engaging social qualities, and he soon became one of Boston's leading social arbiters. His sartorial expressions were extreme. He startled staid Boston by the extremes of fashions he followed. He originated the light blue coat, the brass buttons, and the radiant embroidered waistcoats. His spirited horses attached to a landaulet were driven by a coachman in livery. These and many other acts contributed to make him a marked man, and only his extraordinary ability enabled him to maintain the unusual standards he established. Yet he always searched for the truth, was always open to suggestion, even though he might dislike his informant. He was interested in general science, and when Louis Agassiz came to New England to study the rocks it was Bigelow who went with him to show him where to find the particular geologic strata for which he was searching.

In 1845, Dr. Bigelow was made president of the Boylston Medical Society, and in 1846 his presidential address, "Fragments of medical science and art," was published. In this address he discussed the value of the inductive method of applying knowledge and the use of the senses, in contradistinction to the numerical method, which, he said, made men of science statisticians. In 1847, he issued his famous circular announcing the formation of a charitable surgical institute for outpatients only.

This created a sensation, but his graceful attitude toward the members of his profession, his ability in organization, and his popularity with his clientele made the institution a success.

YOUTH WILL BE SERVED

In 1846, when Dr. Bigelow was only twenty-eight years of age, he was made full surgeon in the Massachusetts General Hospital, a position which he held for forty years. In 1849, he was made professor of surgery in Harvard Medical School, a position which he held for thirty-three years. His hospital and teaching positions enabled him to have a hospital service with beds and patients during the active period of his life. Many of the world's great surgeons have had this advantage. Theodore Kocher was professor of surgery at the University of Berne at the age of thirty-one years, and held the position until his death, a period of forty-six years. Johann von Mikulicz at the age of thirty-two was made professor of surgery in a German university, and held this position brilliantly until his too early death in 1905. In obvious contrast to Dr. Bigelow's opportunities were those of W. H. A. Jacobson. Jacobson was assistant surgeon at Guy's Hospital, London, during his active career and did not become a full surgeon until he was aged fifty-three years. He arrived at the summit of his career late. He retired after but five years of full-time service. Jacobson's book on operative surgery was, in its time in my opinion, the greatest work on this subject that had ever been written. His ripe judgment, clear thinking, dignity, and brevity of expression made his book a classic. I not only read Jacobson's book, but I absorbed it. He wrote largely concerning other people's work, but the critical acumen, the estimations made of the indications for operation and the type of operation were Jacobson's.

Osler's comment on the man under forty years and the man over sixty years caused great merriment and newspaper comment, which has not died out in the intervening years. Osler's philosophy was, in a way, sound. Experience is the great teacher; unfortunately, experience leaves mental scars, and scar tissue contracts. Experience hobbles progress and leads to abandonment of difficult problems; it encourages the initiated to walk on the shady side of the street in the direction of experiences that have been pleasant. Youth without experience attacks the unsolved problems which maturer age with experience avoids, and from the labors of youth comes progress. Youth has dreams and visions, and will not be denied. Sound practices today were only visions the

day they were born. The failure of the Germans in their great attack was due to experience. Germany's leaders were old men, most of them over sixty years; and some of those high in command were over seventy years. The discipline of German life with its military training limited the initiative of its youth, obstructed the progress of thought and invention, and made of many Germans imitators and exploiters of other people's inventions, unfortunately too often without credit when credit was due, the facts concealed by huge smoke screens of scientific pfennigs.

THE WIT OF SCIENCE

Much of the extraordinary success of Bigelow is expressed in his happy saying, "the wit of science," namely, the application of the special senses, in obtaining knowledge and in acting with wisdom. The wit of science not only expresses but actually reveals the science and art of medicine.

In observing the present method of teaching in the medical schools it is seen that attempts are made to teach the student a little of everything. Much of the teaching is so complex that the details cannot be carried out. There is a constant tendency to exaggerate the minute at the expense of the obvious. Not long ago I investigated my old general utility bag which I had not seen for twenty years. As I removed the articles from the bag, one by one, articles I had been taught to use, I questioned my staff of assistants with regard to their use. I found that they were familiar with the articles, but had little knowledge of their practical application. They had not been taught to handle the common tools of their trade in a manner to make them depend on them, but rather to consider them as something apart, to be used by specialists. In my student days less reliance was placed on the stethoscope, that romantic instrument which is the diagnostic sheet anchor of so many men who do not attend the revelation at the operating table or at postmortem.

On the wall of an operating room in Newcastle-upon-Tyne, a room made famous by Morison and now occupied by one of his able disciples, is a legend for the attention of the students. In large letters is written "Eye," in smaller letters, "Touch," and in very small letters, "Ear." One evening, many years ago, the little folk at my house were having a party. I became very much interested in watching their games. A child was blindfolded and two coins were struck together at a distance of about two feet from his head, in different directions. I was surprised

to note that the child was practically unable to tell in which direction the coins had been struck. The explanation for this lies in the development of the special cranial senses. First came the sense of taste that the primitive mouth might recognize food substances. Then came the sense of smell that the primitive mouth might be turned toward food; then the sense of hearing for the protection of the individual, and since danger might threaten from either side or from behind, the ears were placed in the middle of the head. The last of the special senses developed was the sense of sight, and with it came the extensive growth of the cerebral hemispheres, so that while the senses of hearing, taste, and smell are



FIG. 391.—Bigelow medal, obverse.

poorly developed, the sense of sight has a direct pathway to the intellectual organization of the brain. An average man may listen to the description of a piece of machinery that has little meaning to him. If he is shown a picture he instantly obtains a conception of the mechanism, and often a correct one.

The eye, aided by the microscope and the test tube, enabled Pasteur to make his discoveries, the greatest gift ever made to humanity by man. Pasteur's work was vitalized by Lister, and the modern edifice of surgery is erected on the foundation laid by these two men. Asepsis and antisepsis came too late for Bigelow. He had reached the time of

life when new principles were not readily received. This attitude was revealed also in his reception of abdominal surgery, which was making unlooked for revelations under Lawson Tait of England, Jules Pean of France, Joseph Price of Philadelphia, and sturdy, independent John Homans of Boston.

Postmortem investigations of diseases of the abdomen during this period too often showed, not the pathologic condition of the patient during life, but rather the complication from which the patient died. Great confusion naturally resulted in attempts to correlate clinical facts with terminal conditions found at necropsy, that had not existed when the clinical facts were gathered. The return to the hunterian method of pathologic examination under the eye, made possible by means of surgical operations in the abdomen and the other great cavities of the body, and the removal of pieces of tissue for the microscopic study of pathologic conditions during life, led to great advances. Dr. Bigelow, in teaching, made free use of gross pathologic specimens, and one can imagine the effect on his students by his constant recourse to pathologic demonstrations. One may also discern the growth of interest in pathology which resulted in the application of the methods of the study of frozen sections as begun in the Massachusetts General Hospital by Whitney and Mixter, who introduced carbon dioxid as a freezing medium. The quick examination of sections of living tissue, especially since Wilson devised a method for its rapid differential staining, has enabled the microscope to guide the operating surgeon's knife for the benefit of the patient, in a manner as fundamentally different from the examination of mummified dead tissue, several days after the operation, as the work of the operating surgeon differs from the anatomist's dissection of the cadaver.

The wonders of the roentgen ray were yet to come to make the eye supreme. I often think of Sir William Crookes and his untiring efforts in the interest of science. In his attempts to demonstrate a fourth state of matter, Crookes exhausted the air from a heavy glass bulb. When certain electric attachments were made, the bulb became filled with luminous matter and, as Crookes expressed it, "actually touched the borderland where matter and force seem to merge one into another." He named this luminous substance the cathode ray, composed of negative electrons, which is the fundamental conception of the roentgen ray. Crookes also pointed out that when roentgen rays come in contact with solid matter they give rise to shadows, and that the cathode rays,

when outside a magnetic field, always travel in a straight line without regard to the position of the poles. Roentgen's splendid work must not blind us to the fundamental character of the work of Crookes.

ANIMAL EXPERIMENTATION, THE DOCTOR AND THE DOG

Jenner on a certain occasion presented arguments which were capable of being proved, but which he had not proved. The following day John Hunter wrote to Jenner saying, "Why submit hypotheses? Try it on a hedgehog and know." Animal experimentation has resulted in gifts of inestimable value to humanity. The pernicious activities of antivivisectionists seriously threaten the continuance of these investigations, which are of such paramount importance to the nation's health. It is of interest to note that in the last election in California the antivivisectionists, aided by various organized cults, such as Christian Science, osteopathy, and chiropractic, were defeated two to one by a referendum directly to the people, a triumph of an appeal to reason. The defeat of the antivivisectionists was owing in a great measure to the sagacity of Dr. Ray Lyman Wilbur, president of Leland Stanford University. The people, the farmers in particular, were shown what animal experimentation has accomplished in the prevention of disease to farm animals, what it has accomplished for the canning industry in relation to botulism, and the possible effect on economic conditions in California if the work should be discontinued.

It is undoubtedly true that much of the opposition to animal experimentation among reasonable persons has been brought about by a few careless physicians. For at least four thousand years the dog has been man's friend and companion, and the occasional buying of stolen family pets at small prices for animal experimentation, as has been done in some laboratories, has alienated the public. The physician should not be a fence for stolen property, and his complicity cannot be glossed over by saying that he did not know the property was stolen. The physician has no more right to a stolen dog than to a stolen purse. All these difficulties could be overcome by a proper law which would turn vagrant dogs over to accredited institutions. At the present time thousands of homeless dogs, many times more than the number used in all the laboratories of the United States, are killed at the pounds of the various cities, often by methods entailing more pain than any experiment carried out in a controlled laboratory, and are an economic loss

except so far as their hides and fat can be used for commercial purposes. Some method should be devised whereby these animals, or as many as necessary, may become legally available for the use of recognized, responsible laboratories for experimental work.

Moreover, the medical profession in the past has been derelict in permitting untrained men to perform animal experimentation without supervision. It was such experimentation that roused the resentment of a great many persons. If it is the wish of the medical profession to continue this work, its members must not furnish a market for the thief and they must protect the dog from the untrained experimenter. Fortunately, the organized physicians of the country have already made considerable progress in controlling the conditions of animal experimentation from within. Regulations which place upon laboratory directors responsibility for the importance of the problems studied and for the propriety of the procedures used in the solution of these problems have been formulated and adopted by corporate vote in medical institutions throughout the land. By pursuing a policy of honesty and faithfulness to a trust, animal experimentation can be carried on without serious objection. Experiments on animals were performed in Bigelow's time, but today such investigation has become one of the foundation stones of progress.

THE MASSACHUSETTS GENERAL HOSPITAL

M. G. H., as it is lovingly called, was organized one hundred years ago (September 3, 1821). To Dr. John C. Warren and Dr. James Jackson must be given the credit for its organization and for the high character of its service. Dr. Bigelow, during his long connection with the hospital, was ever assiduous in advancing its interests; and under his influence and that of his illustrious colleagues the institution became a great teaching hospital, and its fine traditions have always been worthily maintained. It is fitting in this connection that I acknowledge the debt of gratitude my colleagues and I owe the Massachusetts General Hospital for the kindness, sympathy, and cordial help we have received from its management and staff at all times. In the beginning, the hospital was devoted to charity patients. Admitting day patients and patients who paid was a later event and met with the opposition of Dr. Bigelow, whose mind, acute as it was, did not grasp this new sociological doctrine. The discovery of bacteria and the applications of

this discovery to medicine and surgery brought about a remarkable and sudden evolution in hospitalization, and its beneficent results could not readily be comprehended in Bigelow's time.

American hospital organization in this period was modeled on that of Great Britain's. The caste system, which was the mainstay of the British social structure, was exemplified in its hospital organizations and was the result of the British educational system, which was traditional and calculated to continue the caste. Slosson, speaking of the British government in relation to the universities, justly says: "So in 1874, Sir



FIG. 392.—Bigelow medal, reverse.

William Perkin relinquished the attempt to manufacture the dyes he had discovered because, as he said, Oxford and Cambridge refused to educate chemists or to carry on research. Their students, trained in the classics for the profession of being a gentleman, showed a decided repugnance to the laboratory on account of its bad smells. So when Hofmann¹ went home he virtually took the infant industry along with him to Germany, where Ph.D.s were cheap and plentiful and not afraid of bad smells." Such neglect on the part of England was the fundamental basis of the Great War. The dye industry gave the control of explosives and gases to Germany.

In the early days a hospital was a place for sick persons who had no homes, and for charity patients. This ancient conception of hospitalization did not anticipate modern conditions; it resulted in the denying of hospital care to the honest taxpayer of moderate means, and the extraordinary spectacle was presented of a premium given to inefficiency and laziness. The worthless person was given all the benefits of modern science and of group medicine, which could not be obtained by the average man at an expense he was able to bear. The Massachusetts General Hospital was one of the first hospitals in this country to recognize the rights of all the people to adequate treatment, each contributing as he might be able, the poor to receive as much as the middle class and the rich, but no more.

BIGELOW THE SURGEON AND TEACHER

Given one well trained physician of the highest type and he will do better work for a thousand people than ten specialists. One-tenth of each patient would be treated better by the specialist, but the nine-tenths would have little or no treatment. It is for the next generation to produce, as nearly as possible, the superman who shall have obtained from many special workers the threads of all knowledge to be woven together and applied as a whole for the benefit of the patient. Dr. Bigelow belonged to a generation of men who developed a keen power of observation, and who with the history of a case, and their highly trained special senses accomplished wonders.

Dr. Bigelow's brilliance excelled that of all the group of striking personalities and unusual men of Boston in his day. His career was unexampled in brilliancy and success. In mental acumen, creative vision and swift, unerring and direct action he was unequalled. Probably the essence of his mental powers lay in his ability to concentrate instantly on the vital factor or factors of any problem, and to disregard the unessential details. He picked the kernel of the nut and threw away the husks, to be worked over by others if they chose, or if it fitted into some less important part of the structure he was engaged in rearing. Yet in spite of his apparent disregard for details, no one ever gave greater attention to the essential. This is a characteristic of great men. We think of them as having complex mental machinery. In reality, their mental processes are simple and direct.

Dr. Bigelow's surgical work was thus described by one of his students:

He stood erect and did all his cutting at arm's length. Every stroke of the knife accomplished all and no more than he intended it to accomplish. He used the belly of the knife rather than the point, drawing it with swift strokes as a violin bow is drawn. His hands never fumbled or made uncertain motions; all were direct, unerring, firm, yet delicate. He displayed perfect coördination of mind, eye, and hand. It must be remembered that in Bigelow's time surgery was almost wholly confined to the outside of the body, and thus comparatively limited in scope. However, opportunity was given for dramatic display, and Bigelow liked the applause of colleagues and students. His performance of a lateral lithotomy in the presence of the surgeons from some Russian war vessels was described as being more like a juggler's trick than a deliberate surgical operation. Many of his operations were performed with such swiftness and unerring strokes as to suggest legerdemain. On one occasion, with what seemed an incredibly small number of rapid strokes of knife, saw, and chisel, he removed an upper jaw. In doing this a large artery was opened, a blood-clot formed in the patient's larynx and trachea, and she stopped breathing. Bigelow coolly took her pulse, remarked, "She doesn't seem to be breathing, does she? Well, tracheotomy." The instrument was placed in his hands; in two strokes he entered the trachea, inserted the tube, and blew into it. The patient took a breath, whereupon Dr. Bigelow quietly picked up the jaw and described the lesion in it as though nothing unusual had occurred; his assistants meanwhile secured the wounded artery. His delicacy of touch was remarkable. Sometimes, by merely placing his fingers on a diseased or injured part a correct diagnosis was made. In one instance he passed his finger across a swelling in the sole of a foot and said "fatty tumor," a condition no one else had suspected.

As a teacher, Bigelow's special qualities were those of epigrammatic and dramatic expression and demonstration. His frequent practice of putting a subject in a nut-shell was remarkable. An example worthy of note is as follows: "Gentlemen," said Dr. Bigelow, "many pages have been written describing various more or less complicated ways of treating the shoulder after a dislocation of the joint has been reduced. The whole thing consists of: pad in the axilla, elbow to the side, arm in a sling." He often arranged his amphitheater and his patients with a view to dramatic effect. He was strikingly handsome and distinguished in appearance, which added force and charm to his personal influence. He exercised on his student world the peculiar power and fascination which were the result of his personal attributes as well as of those which he brought to his teaching and to the practice of surgery.

It is to be regretted that our first and second year medical students do not have the advantage of attending the dramatic exhibitions which are the precious heritage of many of the older practising surgeons. In the plastic period of student life, even from the back seats of a surgical amphitheater filled with a spellbound audience, the reading of a case history, the discussion by the surgeon of the details of the operation, and the report of the pathologist, stimulate the student's imagination.

After all, a student will more often carry away a truth, or the essential elements of a surgical case, if it is dramatically placed before him. One of Dr. Bigelow's most distinguished students summed up Dr. Bigelow's characteristics in this forceful paragraph:

If I were to try to sum up Dr. Bigelow succinctly I might say that as a surgeon his remarkable qualities were: A keen diagnostician, an operator of unrivaled dexterity and finished style, a genius in seeing the vital point of surgical problems, possessed of great mental acumen, with the ability to extract the meat from the nut in the swiftest and most telling way, as a teacher remarkable for the power of epigrammatic and dramatic expression and demonstration, thus driving home facts in a most telling manner. These qualities embodied in a man of imposing and distinguished personality, by virtue of which fact their power was greatly enhanced.

Dr. Bigelow had many interests outside his profession, but they were only hobbies. Among these were the restoration of old pictures, soil fertilizers, fancy breeds of pigeons, gems, and the facial expression of monkeys. He dominated the Harvard Medical School and the Massachusetts General Hospital for many years, and up to 1879 or 1880 it was within his power to make or mar the careers of the younger surgeons of Boston; a power which he exercised in many instances.

SURGEONS TRAINED BY DR. BIGELOW

Dr. Bigelow was idolized by his students and admired by his assistants. As an operator, teacher, writer, and originator of surgical procedures, he made a profound impression on the surgery of his day. Yet apparently he never tried to establish a school of surgeons to continue his work. He could not brook competition, and his aid to brilliant students depended on caprice rather than a great surgeon's fixed policy of development. In spite of this, after he retired in 1886 surgeons of his training more or less dominated surgery in Boston. Among his assistants were Dr. C. B. Porter, one of the most skilful surgeons I have ever seen operate; Dr. Richard Manning Hodges, a bold and skilful surgeon; Dr. H. H. Beach, who justly acquired fame; Dr. Arthur Cabot, a sound, honest surgeon of great learning, who made surgical contributions of a permanent character; and by no means least, the brilliant and erratic surgical genius, Dr. Francis Watson, whose contributions to urology, hourglass stomach, and so forth, have placed him permanently in the annals of surgery.

Dr. Maurice H. Richardson, the man whose surgical judgment was

not exceeded by any surgeon I have ever known, was not of the Bigelow school, but it is to be noted that his early training was received in France and that he had many of the Bigelow characteristics.

In appearance and intellectual qualities, Bigelow resembled Theodor Billroth, the great Swedish surgeon who was born in Germany and lived through his contributing years in Vienna. Billroth was the father of initiative surgery, the school that attacked disease in the early stages by constructive effort, not waiting until the advanced stages rendered destructive surgery necessary. Billroth's ambition was to develop great surgeons among his students, and his ambition was realized. Von Eiselsberg, one of his students, is the first of the Teutonic surgeons today. The last time I was in Vienna, just before the Great War, Hochenegg still retained in loving memory Billroth's operating rooms, inconvenient as they were. The lamented Mikulicz, Gersuny, Czerny, and many others I could name called Billroth Master.

Richard Volkmann of Halle, Germany, had Billroth's characteristics. Among his assistants were Kraske, Sprengel, and Schede. Volkmann's death before the Great War cannot be regretted, since he was spared the pain of severing his friendly relations with the English, whom he admired greatly, even to the extent of long Dundrearyish whiskers and English clothes. Volkmann's later years were saddened by a painful affliction. The devotion of his students is exemplified in the distinguished surgeon Fedor Krause, who, during the last years of Volkmann's life, carried on most of his work and maintained his clinic.

Terrier of France was equally distinguished by his students, such as Richelot, Quénu, Broca, Hartmann, Gosset, and Montprofit.

Of Joseph Lister we must say that his students are representatives of Great Britain's best and the world's best.

One of the most splendid examples of the conviction that science comes first, and of the love and devotion to a great cause which transcends the desire for personal elevation, was the Danish surgeon Christian Fenger of Chicago, the Father of modern surgery in the West. Fenger in his best teaching years had only unimportant hospital and teaching connections. But among his students were the late John B. Murphy, the greatest clinical teacher of surgery of my time, M. L. Harris, A. J. Ochsner, and Frank Billings, the distinguished internist whose alert mind comprehends surgical conditions as clearly as the surgeon. My brother or I used to travel each Wednesday night to Chicago to attend Fenger's Thursday clinics and demonstrations. We returned home the

same evening with renewed vigor and stimulus for greater effort. Every year the students of Fenger gather together for a memorial meeting. They do not meet to eulogize, but to stimulate scientific progress, and this is as Fenger would have wished. In a like manner you who were students of Henry Jacob Bigelow, New England's Master Surgeon, propose to perpetuate his name and his work.

THE ENDURING QUALITY OF BIGELOW'S WORK

Henry Jacob Bigelow's importance in the history of medicine will not be exceeded by any American, and will be equaled by few. His recognition and advocacy of ether anesthesia permanently links his name with that of Morton and Warren. Ether was first given for general surgical anesthesia, October 16, 1846, by William T. G. Morton in the clinic of Dr. John C. Warren in the Massachusetts General Hospital, who then removed a tumor from the neck of Gilbert Abbott. The operation was performed before the medical students of Harvard and many members of the medical profession. Oliver Wendell Holmes coined the words anesthetic, anesthesia, and anesthetist at that time. Without the aid of Dr. Warren, Morton might not have had the chance to try out ether anesthesia. The following is quoted from *The Bigelow Memoirs*:

Dr. Bigelow was the unflinching advocate of sulphuric ether as the only safe anesthetic: and his unshaken opinion had a very wide and lasting influence. Bigelow instituted important and productive experiments in anesthesia. He inhaled new and untried anesthetic agents. He made practical and original studies of asphyxia, and thoroughly established the fact that insensibility from the inhalation of nitrous oxid gas is largely due to asphyxia. He was also the first to show that anesthesia by nitrous oxid could be accomplished with certainty only by the use of a large volume of gas; and thus made the way plain to Colton and others for its successful adoption in tooth-pulling and in brief surgical operations.

Dr. William H. Welch, Major General Leonard Wood, my brother, and I were the four medical members of the Electorate of 1920 for the Hall of Fame; and after mature consideration we gave support to Morton on account of the transcendent importance of his contribution of ether anesthesia. The names of Warren and Bigelow, however, must be inseparably linked with that of Morton in connection with ether anesthesia.

The eventual reputation of a man does not depend so much on the average excellence of his work as on matters that are fundamental in the way of inventions and discovery. Dr. Bigelow made two original con-

tributions to the science and art of surgery which gave him lasting fame: the bloodless reduction of hip-joint dislocation by manipulation and litholapaxy.

In 1861, Bigelow published a description for the bloodless reduction of hip-joint dislocations by manipulation. In 1869, he published a complete monograph on the subject. This method is still without a competitor. The greatness of this achievement can be better understood by reading the description of the pulleys and tractors and other instruments of torture which in the pre-Bigelow days, before the use of the anesthetic, were used to force the head of the femur into the acetabulum, and which were usually unsuccessful. Dr. Bigelow's classic description of the anatomy of the hip joint and its relation to the ligaments is one of the masterpieces of American surgical literature. Dr. Bigelow was greatly interested in all types of orthopedic surgery, and as the result of his initiative, Boston has been the world's center of orthopedic surgery for fifty years.

Dr. Bigelow worked on a method for crushing stones in the urinary bladder for about ten years, and finally published a description of the operation in 1878. This operation remains the safe procedure for the nonsurgical removal of cystic calculi. The invention and development of the lithotrite reveals Bigelow's extraordinary inventive genius and mechanical conceptions. He made these, and scores of other instruments himself, for various original purposes. His instruments are still used in the Massachusetts General and other hospitals. His facile manipulation of instruments was that of a prestidigitator. The story is told of his comment at the Boston Museum of Fine Arts that a certain cabinet containing valuable specimens could be unlocked and the contents removed easily. The curator and others present laughed at the idea, said that the case was not only locked but under watch, and that it could not be opened without detection. A few days later Dr. Bigelow, standing with his back to the case in question, picked the lock, removed the specimens and relocked the case, talking the while to his companions, who had believed it could not be done. Bigelow carried the specimens away, and a few days later during the hue and cry resulting from the discovery of the loss, he walked into the museum and handed back the valuables to the officials.

Another medical man produced by Boston, whose name will travel into the future with that of Bigelow, is the late Reginald H. Fitz. Fitz made three monumental contributions to permanent medical literature.

He showed the relation of the appendix to all the infections within the abdomen which we recognize under the general title of appendicitis and its results, the relation of acute pancreatitis to fat necrosis, and the relation of Meckel's and other diverticula to the chain of events which the presence of these congenital or acquired lesions may cause.

Dr. Bigelow, after serving greatly, died, October 30, 1890, in his seventy-second year.

Ladies and Gentlemen: We have met here tonight to review profitably the history of a great life, a life given to service to man, the benefits of which shall last as long as human life exists. I am grateful to the members of the Boston Surgical Society for giving me an opportunity to join them in this expression of appreciation of Dr. Henry Jacob Bigelow.

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THE MEDICAL PROFESSION AND THE PUBLIC*

WILLIAM J. MAYO

INDIVIDUALISM IN MEDICINE

On every side we see the acceptance of an idea which is generally expressed by the loose term "group medicine," a term which fails in many respects to express conditions clearly. In my father's time success in the professions was more or less dependent on convention, tradition, and impressive surroundings. The top hat and the double-breasted frock coat of the doctor, the wig and gown of the jurist, and the clerical garb of the ecclesiastic, supplied the necessary stage scenery. The practitioner of medicine today may wear a business suit. The known facts in medicine are so comprehensive that the standing of the physician in his profession and in his community no longer depends on accessories.

So tremendous has been the recent advance of medicine that no one man can understand more than a small fraction of it; thus, physicians have become more or less dependent on the skill, ability, and specialized training of other physicians for sufficient knowledge to care for the patient intelligently. An unconscious movement for coöperative medicine is seen in the intimate relation of the private physician to the public health service made possible by the establishment of laboratories by the State Board of Health and similar organizations. On every hand, even among laymen, we see this growing conception of the futility of individual effort to encompass the necessary knowledge needed in treating the simplest and most common maladies because of the many complications which experience has shown are inherent possibilities of any disease.

It is well for America that the medical profession has recognized the necessity for organized scientific effort which is taking the place of former competitive medicine. Competitive medicine was the response of the individual physician to his training and environment. It fostered

* Read at the opening of the Cleveland Clinic, Cleveland, Ohio, February 26, 1921. Reprinted from the *Journal of the American Medical Association*, 1921, lxxvi, 921-925.

self-sufficiency and jealousy. The physician has been the council for the prosecution and the defense, the jury, and the judge. It has been necessary for him to acquire the facts, to sum up the evidence, and to give the verdict. Too often the facts that he acquired have been improperly interpreted.

MEDICAL COÖPERATION

Mackenzie points out that medical treatment has always been in advance of knowledge, how treatment has been empiric, even experimental, and that knowledge has come later from the results of unorganized attempts to palliate or cure the diseases of man. The medical profession has long recognized the great value of the facts resulting from the work in clinical laboratories, but only of late has it recognized the great practical value of the labors of the physiologist, the physicist, and other heretofore cloistered departmental workers. The organization of departments of trained workers in special fields of medicine and allied sciences greatly aids in obtaining knowledge which permits a better interpretation of all the facts of the case by the diagnostician and brings knowledge closer to treatment. We can hope that eventually knowledge will precede treatment and that treatment will be based on knowledge, and not, as heretofore, largely on empiricism.

The corrective legislation which reflects the reaction of countries to the manifest failures of individualistic competitive medicine has been like the groping of a blind man. The leaders in these so-called health movements too often have not been members of the medical profession, which has at least all the knowledge and experience extant, but they have been largely politicians, men without knowledge or experience who have taken little advice from those who had knowledge. The general program has been based on an honest attempt to alleviate the condition and diseases of man, but unfortunately it has been based also on the political expediency of an appeal to the prejudices of some classes of voters. These abortive attempts at class legislation in medicine have not given better treatment to the sick man or even more treatment. Let it be said to the eternal credit of the medical profession that the sick have never lacked for medical attention because of poverty. And no matter how many the short-comings of competitive medicine, the medical profession as a whole has always struggled to reduce sickness and to rid the earth of contagious disease; to this, no doubt, is due much of the misunderstanding in legislative bodies with

regard to the motives of the medical profession. The average legislator cannot conceive that any man without an ulterior motive should ask for legislation which would reduce the business on which his livelihood depends.

No group of men is brought into contact with people quite so intimately as the members of the medical profession, yet there is something about this very intimacy which seems to prevent medical men as a whole from understanding mass psychology. The normal human being when well is not conscious of organs; he is little interested in preventive measures to maintain his health, unless sickness either of himself or of his family directs his attention to them. If he is ill he demands a remedy. This is true of public ills as well as physical ills and every session of a state legislature is crowded with bills, remedies for specific evils, usually quack remedies, which do not strike at the root of the evils or prevent the suffering which they cause; for each little political ill a little political remedy is offered, legislative patent medicine. It is difficult, therefore, in the face of the enormous number of immediately annoying, petty ills to secure legislation for fundamental health issues. Of each one hundred dollars spent by our government during 1920 only one dollar went to public health, agriculture, and education, just 1 per cent for life, living conditions, and national progress.

The medical profession as a body is altruistic. Appeals for any purpose of human betterment are made to no class of citizens with greater certainty of ready response than to the medical profession. Collectively, physicians have very little influence. The fact that treatment has for so long a time outrun knowledge, and that with little knowledge there are many kinds of treatment, injures the standing of the medical profession with the public.

HIGHEST INTELLIGENCE A POLITICAL LIABILITY, AND LOWEST INTELLIGENCE A MENACE TO GOOD GOVERNMENT

Dr. Arthur Sweeney, in an article on "The measure of mentality," gives the results of testing the intelligence of 3,000,000 drafted men, grouped according to mental age: Class A, mental age 18 and over, 5 per cent; Class B, mental age from 16 to 18, 10 per cent; Class C, mental age from 14.5 to 16, 18 per cent; Class C, mental age from 13+ to 14.5, 25 per cent; Class C-, mental age from 11 to 13, 20 per cent; Class D,

mental age from 9 to 11, 15 per cent; Class D—, mental age from 7 to 9, 7 per cent.

THE MEASURE OF MENTALITY *

Classes A and B, superior and very superior.		Classes C+, C, and C—, high average, average, and low average.		Classes D and D—, inferior and feeble-minded.	
Mental age.	Per cent.	Mental age.	Per cent.	Mental age.	Per cent.
A 18+.....	5	C+ 14.5 to 16.....	18	D 9 to 11.....	15
B 16 to 18.....	10	C 13+ to 14.5.....	25	D— 7 to 9.....	7
Total.....	15	C— 11 to 13.....	20	Total.....	22
		Total.....	63		

*(After Dr. Sweeney)

In one of Darwin's interesting essays he speaks of the mentality of childhood. The child up to one year of age is a little savage, biting, kicking, striking, without regard to personality. After this period, up to five or six years the child has no regard for the right of property. One child will take a plaything away from another, recognizing only force. Between the ages of seven and thirteen years the child displays well developed feudalistic tendencies with clan leadership; this is the Boy Scout period during which children are organizable and obedient to their leader. Notice how closely this 7 to 13 normal mental age of childhood corresponds to classes C—, D, and D—, which shows that 42 per cent are mentally children. Persons below average intelligence can be organized into groups which are easily led by specious argument, and therefore under cunning leadership they exercise political control entirely out of proportion to their numbers. On the contrary, Classes A and B, 15 per cent, composed of persons of high mentality, cannot be organized; there is almost nothing on which they will agree collectively, although individually they may act intelligently and often with altruism. This group comprises the persons who are vigorous critics of public measures, but who will not vote; they are full of precept without example, pacifists, pink socialists, antivivisectionists, and so forth, of little worth politically. These have ever been the ardent supporters of cults and quackeries. Politicians appreciate this fact and as a group consider the political influence of persons of the highest intelligence to be negligible. Many men elected to hold office would like to act wisely and in the interest of the public, but they receive no real support from the so-called upper class and thus are forced to become politicians and appeal to the lower class. The men elected to our legislatures may be

said to be of at least average mentality. To be effective, power and responsibility must go together. While the legislators have great responsibilities they have little power to act independently. The power which controls them is the organizable political power which represents the lower order of intelligence. We should not complain if the least intelligent exercise the privilege of the ballot. Rather let us say that they appreciate the ballot more than the so-called intelligent, and in this respect at least are better Americans. A great political burden is thrown on the average man. The high average, the average, and the low average man form 63 per cent of the total number of male voters. These are the common people who face life's sternest aspects and with this experience are often enabled to act with superior political intelligence. These people are, all in all, the best friends of the medical profession, and to them we must appeal. Persons in Classes D and D- (22 per cent) do not think intelligently, but they act, and usually under bad leadership. The ignorant negro vote has been eliminated in the South, but congested in Northern cities it is a menace to good government. Is it wise to put the loaded gun of the ballot in the hands of persons who are mentally children, and of aliens who have no racial sympathy with Anglo-Saxon institutions? Education will do much but not everything to remedy the situation. Men are not born into the world intellectually equal. Equal suffrage doubles the electorate and introduces an element of the highest importance into the political life of the nation. Women are more conscientious than men, and as a group less organizable. They appreciate education, sobriety, and peace. The life of a woman centers in the home and she can be depended on to do everything possible to benefit the home. The medical profession must present medical problems to the woman and to the average man.

FUNCTIONAL NERVOUS DISEASES THE SMOKE SCREEN OF QUACKERY

We cannot blind ourselves to the fact that functional nervous conditions may closely mimic physical conditions. Neurasthenia, psychoasthenia, hysteria, and allied neuroses are the causes of more human misery than tuberculosis or cancer. The tuberculous patient is always happy and "getting better," and at least the cancer patient comes to a termination of his miseries. My brother once said, "The neurasthenic enjoys bad health; the family and friends suffer." Our knowledge of all the nervous conditions which we have not proved to be physical is slight,

and for their treatment an enormous number of quack remedies is used outside the medical profession, and unfortunately inside as well. To quote again from my brother, "All varieties of game are protected by a closed season. There is no closed season for the neurasthenic." The medical profession as a whole has not realized that for all practical purposes the cerebrospinal nervous system represents man, and that man is not so much concerned with whether his suffering depends on physical disease as he is with the fact that he suffers. The suffering is real to him whether or not it is real to the medical man. Social conditions are the common cause of disaster to an unstable nervous system and lie behind the bulk of the nervous disturbances which mimic physical conditions, breed neurosis, and result in sorrow and misfortune. The patient demands a remedy, not prevention. Perhaps life obligations are the fundamental cause of the disturbances, and we cannot change the social condition of our patient. If relief is given, it must be through change of mental attitude; after all, life is what we believe it to be and happiness is a state of mind, not necessarily a state of body. In homeopathy mental suggestion appeared in the simplest form and was often effective in the treatment of functional disorders. We must remember the fact that most diseases are self-limited and that nature tends to cure rather than to destroy. High dilutions, in two glasses, a teaspoonful each hour taken alternately, pleasantly suggest betterment. The opposition of the regular medical profession lengthened the days of homeopathy, but shortened the days of so-called "allopathy," whose nasty medicines induced the patient in self-defense to get well. Today homeopathy is a part of regular medicine, its follies have been dropped and the good added, and the sons of homeopathic practitioners, like the sons of the allopathic and electric practitioners, are studying regular medicine which is broad enough to contain all honest searchers for the truth in medicine.

Christian Science has capitalized and commercialized the mentally healing virtues of Christianity. Among all peoples in all times the prevailing religion has been successful in relieving sickness so far as mental suggestion could give comfort or indirectly affect the physical condition. To comfort the sick and those afflicted mentally as well as physically has been the great function of religion, and we see this effect in all its variations, from the cheering up of the downcast to the production of the hypnotic state. The great opportunity of Christianity lies in the moral, mental, and physical misfortunes of man. I

venture to say that people of this generation have not had the comforts of religion received by people of earlier generations. Religion is no longer such a potent force in the sick room; I would not presume to say that too much time has been put on the state to come, but there appears to be a distinct loss of relation to the state of the living. In this field, so sadly neglected by the protestant churches, Christian Science, while wholly devoid of science, at least brings the comfort of religion to bear on a great number of human misfortunes. If Christian Science would confine itself to mental and functional disturbances of man it might do more good and less harm. The very absurdity of the book, "Science and health," has aided perhaps in obtaining effect; possibly one might say that the unstable type of mind nowhere better expresses itself than in the book "Science and health," in which an appeal is made to similar minds of persons similarly situated. Gazing at the pages of this book apparently has the same effect on the reader that gazing on the crystal ball has on the subject of the hypnotist. Not all persons have sufficient imagination to accept the Christian Science jumble. It takes real imagination to reach a hand into the air, bring it down empty and say, "See what I have in my empty hand."

It is said that the Chinaman and the East Indian worship wooden images, but they do not. To them the images are emblematic, and they need those physical emblems to bring the mind to bear on the religious side. Religious forms and ceremonials aid in impressing on the mind eternal truths. For people lacking in imagination and to whom Christian Science cannot appeal, there are a host of other cults, each with its remedy, in which sufficient of the physical is present to give body to mental effect.

Osteopathy appears to be a combination of mental suggestion and certain definitely valuable mechanical practices. Anterior poliomyelitis once was called "The Scandinavian disease" because of its ravages in the Scandinavian countries. In Sweden massage was highly developed, and for years trained masseurs have been doing much for certain types of physical disabilities. The war has taught the medical profession the great value of active and passive movements and how much can be accomplished thereby in suitable cases of disorders of the muscles, bones, and joints, and such treatment is now recognized medical asset. Osteopathy, with all its absurdities, therefore, has had a certain degree of usefulness in this field, until recently neglected by the medical profession, but it has depended largely on suggestion for its effect. This

cult has tried to improve its educational basis, but it is doomed. To tell a man that his ribs or knees or other visible parts of his anatomy are dislocated may be credited for a time, but if he compares those parts of his anatomy with those of members of his family, or perhaps joins a Y. M. C. A. physical training class where he may see other men's ribs and knees, he loses faith because the absurdity is evident. Poor osteopathy! Chiropractic has stepped in and taken the spine out of osteopathy. Every man knows that he has a spine, but it is behind him, he cannot see it, and therefore he cannot get those enlightening comparisons open to most patients of osteopathy. Chiropractic simplifies the whole theory and practice of osteopathy. The barber, the underpaid minister and teacher, and the clerk quickly acquire the jargon in chiropractic schools for a price. Chiropractic does less good perhaps than osteopathy, but it has a better alibi, with a shrewder conception of the possibilities of concealment of the absurd. Can we wonder that the public at large fails to appreciate the essential differences between what we speak of as functional nervous diseases and their mimicry of the physical, when we as a profession have so little knowledge concerning these matters? In these cults is represented treatment without knowledge, in response to the desire of the people for a remedy for existing ills, real or imaginary. The patent medicine business is based on the desire for a remedy and faith in a suggested cure. The public is satisfied with each new cult until its failures become known. Hope springs eternal in the human breast, and quack remedies and cults with new names take the place of the old.

As one looks, then, to the future of medicine he sees the necessity of the earnest study of the relation of the nervous system not only to disease but also its relation to unhappiness in all forms, resulting from all causes. It is trite to say that the public must be educated, when our own education is incomplete, our knowledge small. This problem is being attacked from many sides. The educational health work of the Rockefeller Foundation and other well known philanthropies in the elimination of the hookworm, and mosquito-borne, and other diseases, has been heaven sent and has helped every state in the Union to create health legislation for the public good. Individually persons will pay for a remedy for existing ills, even for treatment without knowledge; but collectively the public will not give money until knowledge outruns treatment by a margin so great that all may see and be convinced.

THE MEDICAL PROFESSION AND THE PUBLIC

The striking feature of the medicine of the immediate future will be the development of medical coöperation in which the state, the community, and the physician must play a part. Just how shall this coöperation be effected? If conditions are studied as they exist abroad, the tendency will be found to develop so-called class health legislation. In Germany it was believed that health legislation would lead to earlier recognition of disease and better care of the sick workman and his family. Injuries and all kinds of disease were to be greatly reduced in amount and lessened in effect, but the results were anything but desirable. The plan did not lead to better care of the sick; they were cared for as badly as before. Doctors who could not make a living in any other way were obtained, chiefly, to fill the places created. As there was a certain element of free choice of physicians by the sick beneficiary, the doctor had to please the patients in order to hold the job. The system led to malingering which the honest physician could not check if he tried, and the result was that he lost his patient to an unscrupulous competitor. This form of dishonesty became so prevalent as to be a public scandal. Disability from sickness was not reduced, but rather increased. The man with an injured finger who could have been a part time producer within a week did nothing until his finger was entirely well, perhaps for two months. There was no medical coöperation to give better care. In England the same plan is in use with the same results. Patients who were treated by physicians without charge before are now treated as badly at the expense of the taxpayer.

It is very evident that health insurance, while sound in theory, has not taken human nature sufficiently into account. The early organization of our hospitals shows the same one-sided tendency. American hospital organization was modeled on that of Great Britain. In the early days a hospital was a place where persons who had no homes, and charity patients, could go when sick. This ancient conception of hospitalization did not anticipate modern conditions. The continuance of this outgrown practice resulted in denying hospital care to the honest but poor taxpayer, and we had the extraordinary spectacle of a premium given to inefficiency and laziness, special hospital privilege for the unproductive person who was a liability instead of an asset to the community. The worthless were given all the benefits of modern

science and group medicine which could not be obtained by the average man at an expense which he was able to bear.

I could never quite understand the viewpoint of the man who leaves a large amount of money for a charity hospital. The care of the poor and the unfortunate is as much the duty of a city as taking care of the streets or the sewers or the water mains. The community will do only those things which it must do. There is no more reason why a man should give money to relieve the taxpayers of this just burden than there is why he should pay for the street paving or perform any other public function. What he should do, I believe, is to step in at the point where the public cannot or will not expend money, that is, to advance knowledge by research and investigation which will prevent sickness in the future, and furnish better care for patients suffering from certain diseases which require more study than is given in the average municipal hospital. If hospitals are to be a part of a plan of philanthropy, at least let their benefits be for all classes of the community, each patient contributing a just proportion of the expense according to his means; in this way is forwarded the cause of true Americanism, in which each man is taught to be self-supporting and to pay, so far as he is able, for what he gets, rather than to encourage mendicancy.

To sum up these reflections on the relation of the public to medicine I have at least a few words of comfort. I donned the uniform during the war, knowing that we as a nation were 100 per cent right and believing that we were at least 90 per cent efficient. The war ended: I still have my faith that we were 100 per cent right, but my idea of public efficiency has dropped from 90 to about 50 per cent. Individually the American is the most efficient man on earth, collectively and politically, extraordinarily inefficient. Many varieties of human selfishness reduce our efficiency to a low point, yet at heart 85 per cent of American people are sound. The medical profession made a great record in the war. The degree of medical efficiency was higher, in my opinion, than that of any other similar body of men, and there was no medical scandal. This was largely due to the leadership of Surgeon-General Gorgas and of Surgeon-General Ireland. The average human being, however, distrusts trained ability and skill in every department of life, and much of the difficulty that was encountered in caring for the sick soldier was due to this distrust, the result of ignorance and prejudice. And yet America functioned on not much better than 50 per cent average intelligence and was the greatest single factor in the

ending of the war, and this was by reason of character and ideals, what Bismarck called the "imponderables." We can weigh many things, but not the result of human sentiment. America is today successfully functioning on the average intelligence which is steadily growing as the result of publicity, a form of education to which the American is most responsive. Russia today is sadly functioning on the average intelligence of Russia; England and France are functioning on the highest intelligence. Their political systems afford an opportunity for service to their great men. Pierce Butler, one of the leading members of the American Bar Association, once remarked, "Under an autocracy the Ship of State glides smoothly through uncharted political seas, but when it goes on the rocks everyone on board is drowned; while under a republic the passengers' feet are wet all the time, but the Ship never goes on the rocks." There is much to be hoped for and much to be expected from a better understanding of medicine by the American public.

FROM THE ABSTRACT TO THE CONCRÈTE

The medical profession can be the greatest factor for good in America. The greatest asset of a nation is the health of its people. Our failures as a profession are the failures of individualism, the result of competitive medicine. The real job of the medical profession is the extension of knowledge of what the medicine of today is doing and can do in the future, and this must be done by collective effort. A frank recognition of the necessity for coöperation is necessary. One of the signs of the times is the development of such institutions as the Cleveland Clinic. Such an institution recognizes the rights of the sick man to more careful treatment. It recognizes that the cause of the sick man in this and future generations depends on education and research, and it provides that these things shall be done not only as the result of philanthropy but also as a well thought out self-supporting plan under the guidance of the medical profession. Clinics of the nature of the Cleveland Clinic cannot be organized generally, but community of medical interests can be established everywhere. As I have previously pointed out, a medical building with a medical library where physicians can meet, common access to laboratories containing modern means of diagnosis with good technicians in charge, the whole managed and controlled by the physicians of a community, would enable every patient, rich or poor, to obtain proper treatment. A basic fee, like a club due, may be charged

each physician, the remainder of the expense to be divided in proportion to each member's use of the equipment. Arrangements for mutual consultations for early diagnosis and for the proper handling of emergency cases should be made. The city's health and institutional work should also be cared for by the medical group at a decent remuneration and the unexpended proceeds devoted to bettering the medical equipment. All these desirable arrangements may be possible by coöperation between the physicians of a community.

Properly considered, group medicine is not a financial arrangement, except for minor details, but a scientific coöperation for the welfare of the sick. Medicine's place is fixed by its services to mankind; if we fail to measure up to our opportunity it means state medicine, political control, mediocrity, and loss of professional ideals. The members of the medical fraternity must coöperate in this work and they can do so without interfering with private professional practice. Such a community of interests will raise the general level of professional attainments. The internist, the surgeon, and the specialist must join with the physiologists, the pathologists, and the laboratory workers to form the clinical group which must also include men learned in the abstract sciences, such as biochemistry and physics. Union of all these forces will lengthen by many years the span of human life and as a by-product will do much to improve professional ethics by overcoming some of the evils of competitive medicine.

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